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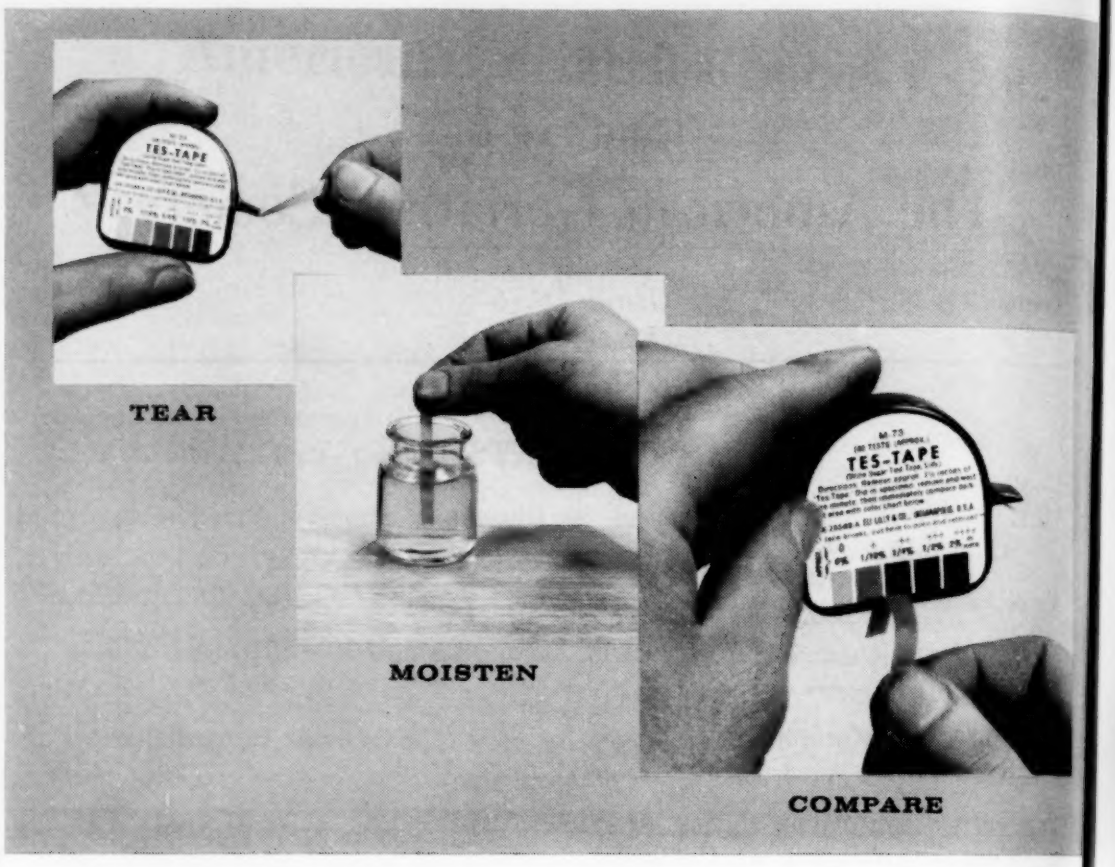

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PATHOGENETIC AND ALLIED INFLUENCES IN CHRONIC PULMONARY EMPHYSEMA*

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Pulmonary emphysema means inflation of the lungs. The terms is generally used to describe a chronic disease which, in its fully evolved state, is readily recognized as a characteristic clinical entity. It has been called hypertrophic or vesicular emphysema to draw attention to the progressive distention and rupture of the alveoli, and chronic obstructive emphysema to emphasize the importance of bronchial constriction as a major cause of the clinical symptomatology. Other forms of pulmonary emphysema have been described, such as acute physiologic emphysema in which hyperinflation of the lungs takes place as a result of severe physical exercise, or acute vesicular emphysema in which there is temporary overdistention of the alveoli as a result of bronchial obstruction, either localized (as from foreign bodies and tumors) or generalized (as in protracted bronchial asthma).

Senile emphysema is not characterized by over-inflation of the alveoli. Landis states, "In the strict sense of the word this is not a true emphysema at all. . . . It is but one of the atrophic changes commonly met with in the aged." In Laennec's classic description of emphysema, the senile type was not included. The hypertrophic obstructive entity with which this presentation is concerned is characterized by increased lung volume, impairment of elastic recoil, bronchial obstruction and inefficient alveolar ventilation, in contrast to the tendency to decreased lung volume, comparatively slight reduction in elastic recoil and unobstructed bronchi in atrophic, so-called senile emphysema. Although senile emphysema is more fully discussed by Bickerman, I wish to emphasize that the cause of shortness of breath is not simply related to the loss of vital capacity, the moderate impairment of elasticity of the lungs, the decrease of the alveolar breathing surface, or impair-

* From Barach, A. L., and Bickerman, H. A.: Pulmonary Emphysema. Baltimore, The Williams & Wilkins Co., to be published, 1956.

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ment of diffusion, but, as reported by Rappaport and Mayer, is due to the progressive decline in physical activity. In fact, these authors, believing that functional disuse is the most important factor in the pathogenesis of emphysema, state: ". . . the involutional lung defect present both in chronic pulmonary emphysema as well as in senile emphysema is the result of progressive disuse of the organism and hence is functional in its origin as well as in its nature." Whether a developmental so-called "involutional lung defect" is or is not involved in the pathogenesis of chronic pulmonary and senile emphysema, it is becoming steadily more clear that decrease in physical fitness plays a markedly important role in aggravating the symptoms of both diseases. Constant physical training is required to maintain the pulmonary reserve of normal individuals at its peak capacity. Consideration will be given later to the restoration of respiratory function in patients with pulmonary emphysema who perform daily exercises during the inhalation of oxygen and thereby undergo a physical training program not possible for them to achieve when breathing air.

Monroe, in an extensive clinical and pathologic study of individuals over 61 years of age, emphasized the disagreement between the clinical and pathologic diagnosis in respect to pulmonary emphysema. He stated, "Finally, an important cause of breathlessness during and shortly after effort is merely physical unfitness. It is difficult to guess its frequency in this group from hospital records, but the experience of the Geriatric Clinic and the practice outside the hospital is that it is common." Of 129 autopsies in his study the clinical diagnosis of emphysema was omitted from the pathologic summary or stated to be insignificant in 110 cases (85 per cent); however, in 14 cases (11 per cent) advanced emphysema was found post mortem, but the clinical diagnosis had not been made. Richards states that chronic pulmonary emphysema of significant anatomic extent is found in about 5 per cent of all autopsies. Schlesinger, reporting on aged patients, said that in 666 autopsies evidence of marked emphysema was present in one third and definite evidence of some emphysema in fully half; this series included hypertrophic and atrophic pulmonary emphysema in equal proportions. The increasing prevalence of pulmonary emphysema may be explained by better methods of diagnosis and by increased longevity of both men and women. Amberson summarized the situation as follows: "Practically all aging people develop some degree of pulmonary emphysema and frequently there are changes such as pulmonary emphysema and frequently there are changes such as pulmonary fibrosis, chronic adhesive pleurisy and chronic bronchitis. Dyspnea is the most common symptom and is the mechanism whereby ventilation of the lungs is maintained as nearly as possible at normal levels. It is the cause of the physical limitation and tendency to fatigue which these people experience. If ventilation of the lungs and gas exchange cannot be maintained at the physiological level, chronic anoxia results. This aggravates the symptoms mentioned and may result in irritability, weakness, anorexia and impairment in general tone and nutrition. Susceptibility to respiratory infection is greater in the emphysematous than in healthy people."

Since the brain is the organ most sensitive to lack of oxygen, the fact that hypoxia, either at rest or on exertion, is more common in pulmonary emphysema than in any other chronic ailment justifies the discussion which will appear in our

book on the effects of hypoxia on mental function. Mueller-Deham states: "In all old people emphysema is one of the chief agents in lowered physical capacity and the deterioration of the latter is in direct ratio to the severity of the emphysema." The importance of maintenance of body tone and pulmonary reserve by cultivating suitable physical exertions by breathing exercises and by a suitable oxygen exercise program is emphasized because these considerations apply to people in the middle-age as well as in the older-age group.

PATHOGENESIS OF PULMONARY EMPHYSEMA

The pathogenesis of pulmonary emphysema is obscure in most instances. It occurs four to five times more commonly in men than in women. The writer has observed several cases which followed two to six months after an attack of atypical pneumonitis. Exposure to certain dusts produces pulmonary fibrosis, which is frequently accompanied by some degree of pulmonary emphysema. Other conditions in which a high incidence of the illness is found include chronic pulmonary infection, bronchial asthma, chest deformities, bronchiectasis, pulmonary arteriosclerosis and chronic bronchitis. The atrophic changes associated with loss of vascularity of the alveoli and dissolution of the alveolar walls may be in part caused by a primary ischemia, or an obliterative endarteritis, or these changes in themselves may represent a primary degenerative phenomenon with secondary vascular changes.

Conditions which produce sustained hyperinflation of the alveoli are to be considered as predisposing causes, especially in the presence of a pulmonary parenchyma that is impaired as a result of infection, circulatory abnormalities or constitutional predisposition.

The increased intrathoracic pressure developed to overcome resistance to the flow of air, especially during rapid breathing and cough, may result in undue strain on alveolar walls not supported by the opposing pressure of the thoracic cage, namely in the apical regions. Trapping of air in dilated alveoli leads to their progressive distention when premature bronchial closure cuts off the expiratory stream of air, especially under circumstances in which bronchial constriction is enhanced because of inflammation of the mucous membranes, presence of occluding exudate in the bronchi, or increased tonus of the bronchiolar muscles—the latter's effect being exaggerated by diminution of the recoiling tension of lung parenchyma which in normal individuals tends to keep the bronchi open.

Stretching of the lungs at the periphery of the chest during violent inspiratory efforts is probably a major factor in tearing of the alveoli and formation of bullae. Due to the characteristic overinflation of the lung, the flattened diaphragm pulls the lower thorax inward, the last five intercostal muscles being apparently not sufficiently forceful to expand the costal margins under these circumstances. Aeration of the lower lobes and the hilum is thus impaired and ventilation is then carried on by expansion of the upper thorax, which is pulled upward and forward by the upper five intercostals and the accessory muscles of respiration. The force of this type of chest expansion, experienced on the alveoli nearest to the point of change in volume, appears to exert a damaging influence.

Cogent as this reasoning appears to be, it does not explain the frequency of

bullous formation in the lower lobes of the lung. Perhaps other factors are operative here, such as an increased tendency to bronchial obstruction and infection due to the stagnation of secretions in the dependent parts of the lungs. In addition, areas of the pulmonary parenchyma deprived of adequate ventilation may also be secondarily subject to chronic impairment of circulation, with resultant atrophic changes. It is embarrassing to rigid adherents to the inspiratory theory of alveolar stretching and tearing during lung inflation to explain the presence of a markedly emphysematous lower lobe which is little moved by either the diaphragm or the lower ribs, even though similar reasoning seems applicable to the periphery of the lung near the upper half of the chest.

It is noteworthy that the parenchyma of the lung near the hilum frequently contains well preserved alveoli that are also perfused with blood. The value of restoration of diaphragmatic function, even when of limited degree, is dependent upon the resultant ventilation of the hilum, at the expense fortunately of wasteful disposition of air to bullous areas where respiratory exchange is notoriously inefficient. Emphasis shall, therefore, be placed on selective rather than on total pulmonary ventilation. Liebow has recently emphasized that renewed consideration should be given to the expanded venous shunts between the right and left side of the heart, as well as to the increased bronchial arterial circulation and the anastomoses of the two arterial systems in pulmonary emphysema. The bronchopulmonary venous circulation was found to be greatly expanded in his studies. In regions of the lung in which the pulmonary veins are shut off, the blood may be shunted into the bronchopulmonary veins. Although the direction of flow is probably from the left to the right auricle the valves of the azygos and the bronchopulmonary veins may lose their competency in advanced emphysema and the flow may then be reversed. As a result of the obliteration of the pulmonary arterial and capillary blood the bronchial arterial system becomes immensely expanded, with large precapillary anastomoses appearing between the two arterial circulations and with a high-pressure systemic circulation in direct communication with the low-pressure pulmonary circulation. Unsaturated blood from the pulmonary artery may bypass the diseased parenchyma to a considerable extent. These communications, in addition, represent points of resistance that may play a role in the development of arterial hypertension.

The small blood vessels of the lungs are not subjected to the normal variations in intrapleural pulmonary emphysema, a condition which tends to impair the flow of blood into the pulmonary venules rather than the bronchial veins, as ordinarily occurs during each inspiration. It has also been emphasized by Loeschcke and confirmed by Liebow that the bullae of severe emphysema are in fact expanded parts of the bronchial tree more proximal than the alveoli, including the respiratory bronchioles and bronchioles themselves. The musculature surrounding these structures is often markedly hypertrophied. The drainage of these structures is by way of the bronchopulmonary veins which, placed within the walls of relatively rigid bronchi, may well be less affected by changes in intrapulmonary pressure. Liebow has acknowledged that the quantitative factors of blood flow in the lungs of patients with chronic pulmonary emphysema and pulmonary fibrosis

are difficult to analyze but he mentions the interesting fact that in experimental dogs ligation of the pulmonary artery results in a collateral flow approximately one third of the right cardiac output.

Chronic bronchitis is the most frequently associated condition. In a small number of cases an infectious process may be demonstrated by the presence of pus in the sputum, with or without local or generalized bronchiectasis. In the larger number of cases the expectoration is mucoid and scant. In those instances in which bronchial asthma is also present, the sputum is more viscid and the cough more frequently accompanied by wheezing and difficult respiration (especially in attacks of a paroxysmal nature) rather than by a more or less continuous bronchospasm with periods of relief induced by bronchodilator agents.

In patients in whom the factor of paroxysmal bronchospasm is conspicuous, there may be an allergic etiology for the increased severity of the disease. In fact, there are instances in which the primary diagnosis, bronchial asthma or pulmonary emphysema, is difficult to make since manifestations of both conditions are clearly evident. In such cases, a careful search for extrinsic factors to which the patient may be hypersensitive is indicated. Since bronchial asthma does occur in patients with pulmonary emphysema, the elimination of irritant inhalants, revealed by clinical history or by skin tests to produce bronchospasm, will manifestly reduce bronchial constriction and alveolar overdistention. Desensitization procedures in this group (including the use of pollen, dust and bacterial antigens) may have an effect similar to that achieved in patients with uncomplicated bronchial asthma; but in the more commonly observed case in which prolonged bronchial constriction plays an important role but in which the symptoms of paroxysmal bronchial asthma are absent, the existence of an allergic diathesis as the cause of the mucoid expectoration and bronchospasm is difficult to demonstrate.

If it be accepted that bronchospasm itself constitutes an indication of allergy, then the condition would be interpreted as allergic in origin. The results of investigations from an allergic point of view, however, are generally negative in most patients with diffuse obstructive emphysema; the skin tests reveal no significant reactions and the clinical history does not as a rule provide a clue to hypersensitiveness to those agents that are admittedly factors in uncomplicated bronchial asthma in younger patients. In older asthmatic people, the condition is frequently accounted for on the basis of bacterial allergy, in the absence of the finding of extrinsic factors, and treatment of the patient consists of attempts to decrease the hypersensitiveness to bacteria by increasing doses of vaccines made from pyogenic micro-organisms—generally with the joint use of house dust. This approach, however, has not been advocated for the patient with chronic pulmonary emphysema, unless he suffers in addition from bronchial asthma and suitable investigation has resulted in the finding of a clearly demonstrated allergic factor.

The pathogenesis of the disease may, in time, become more clear by projected studies on the remarkable relation of respiratory infection to an exacerbation in the symptoms of the disease. Following a common cold or viral pneumonitis, a prolonged period of increased dyspnea is characteristic, even in cases in which pyogenic infection does not take place. It seems difficult to ascribe this reaction

simply to bacterial allergy. In any event, other influences are actively involved which impair respiratory function in addition to the increase in bronchospasm. Inflammatory swelling of the bronchiolar mucous membrane, as a result of virus infection or subsequent pyogenic invasion, undoubtedly results in a further increase in constriction of the smaller air passages. The increased exudate itself, at first mucoid and at times later purulent, adds another factor in the production of obstructive dyspnea. The elastic recoil of the pulmonary parenchyma, which tends to keep the smaller bronchi patent in expiration, may itself be damaged by infection. The ventilation becomes less efficient, hypoxia tends to be aggravated, and an increased strain on the circulation may play a role in some cases, especially in the group of patients discussed by Richards and Fishman, in whom cardiac insufficiency became evident.

Physiologic studies have made it abundantly clear that any process which increases the degree of bronchiolar constriction enhances alveolar overdistention, with progressive impairment of respiratory function. Concerning the allergic aspects involved in the pathogenesis of pulmonary emphysema, a summarizing statement may be made that when there is good evidence of a clear cause-and-effect relationship between an extrinsic allergen and the production of bronchospasm the therapeutic approach should include the use of such knowedge as the allergist may make available. However, the fact that the symptomatology of pulmonary emphysema is made worse by upper respiratory infections should not be considered as evidence that the presently employed desensitization programs are effective in decreasing the state of so-called bacterial allergy. It is generally agreed that food rarely plays a role in the production of an allergic state, insofar as it may be reliably revealed by skin tests. In those instances in which bronchospasm consistently follows the ingestion of a specific food, the patient is generally aware of the relationship.

That posture is involved in the pathogenesis of chronic pulmonary emphysema has been maintained by Heckscher who, after reviewing the older literature, emphasized that the erect military position is responsible for keeping the lungs in a more inspiratory and hence more constantly inflated state; the vital capacity was found to be decreased and the residual air increased, even in normal men, when the subject moved from an easy standing to an erect lordotic position. In other discussions on senile emphysema the mechanism of production of the disease has been attributed to a different change in posture, *i.e.*, one caused by a degeneration of the intervertebral discs of the dorsal spine, manifested at first by swelling and later by collapse with destruction of the cartilage. In this so-called postural emphysema the antero-posterior diameter of the thorax is increased, which gives it a barreling appearance; but impairment of respiratory function is not considered to take place unless the condition is accompanied by obesity. Under the latter circumstance, Kerr described the production of dyspnea, defective pulmonary ventilation and in some instances subsequent cardiac failure. With increase in obesity, the weight of the abdomen moves the line of gravity forward in the erect posture and, as compensation for this, the major portion of the dorsal spine is moved backward and the thoracic curve becomes exaggerated.

A barrel-shaped chest occurs as a result of the increased thoracic curve, and the diaphragm is pulled downward by the increased weight of the abdominal viscera. The poor excursion of the diaphragm lowers the vital capacity and the tidal air, which results in the shortness of breath in the standing position referred to by Kerr as "orthostatic dyspnea."

The increased lordosis of the dorsal spine produced by military training, in which the shoulders are drawn backward and the guts sucked in, results, according to Heckscher in a tightening of the abdomen and impairment of diaphragmatic descent, with consequent over-inflation of the alveoli. The erect standing position does indeed increase the severity of dyspnea in patients with pulmonary emphysema; they breathe better leaning far forward or even walking on all four extremities. Sometimes these patients are seen to squat with the lower abdomen pressed against the thighs which, in itself, raises the diaphragm. Alexander and Kountz pointed out that exerting pressure with the flat of the hand just above the symphysis pubis, or with a properly designed belt, raises the diaphragm to its normal position of relaxation and in that way restores a certain amount of diaphragmatic respiration. It is clear that in the erect military posture the viscera exert a downward pressure on the diaphragm, which is a handicap when there is impairment of elastic recoil of the lungs. As the patient either sits or walks in the bending-forward position, there is a diminution in gravitational force of organs attached to the diaphragm opposing its ascent during expiration. The relaxation pressure of the lungs is further enhanced as the patient moves from the head-up to the head-down position.

I have outlined some of the factors in the pathogenesis, or at any rate in aggravation of the symptoms of chronic pulmonary emphysema. Our colleagues will present their specialized knowledge concerning a variety of basic sciences frequently involved in this syndrome, as well as information that may be used in the treatment of the individual patient. A certain amount of overlapping of material is inevitable, since this clinical entity will be presented from various physiologic and therapeutic aspects and because expression of different points of view is intended. An account of pulmonary emphysema by one writer would undoubtedly have resulted in a more harmonious picture of the mechanism and therapy of the disease but in the present state of our knowledge a uniform picture might well be misleading. Although recent studies on the physiologic aspects of respiration and circulation have resulted in several clinical applications in medical practice, the interpretation of the precise mechanism whereby the improvement takes place has resulted in considerable difference of opinion.

The increase in the use of corticotropin, cortisone and, recently, prednisone has resulted in a more powerful control of bronchospasm than was possible with the agents previously employed, but at the cost of hazards not formerly present with the use of conventional bronchodilator agents. A similar situation has arisen with the advent of more powerful antibiotic agents in the control of chronic infection.

I have said nothing up to this point concerning the effect of emotional influences in respect to the pathogenesis or even modification of the severity of the

disease. Although no one could stretch his imagination to the point of thinking of pulmonary emphysema as a psychosomatic illness, in the sense that one might conceive of irritable colon or nervous indigestion, it is now clear that certain forms of hyperventilation result in trapping of air in alveoli and overdistention of the lungs. There is also evidence that certain emotional states precipitate bronchospasm. That anxiety can be the mechanism productive of an injuriously heightened pulmonary ventilation and consequent overinflation of the lungs, with impaired respiratory function, seems to the writer unquestionable in some cases. On the other hand, certain pleasurable forms of excitement and exercise, even when accompanied by hyperventilation, have consequences that appear more beneficial than a life which is too pastoral. Schutz, in a paper recommending muscular exercise in patients with bronchial asthma, called attention to the observations of Selye on the therapeutic effect of muscular exercise in respect to its stimulating effect on the adrenal cortex, as well as the desirability of a certain amount of adventure, capable of arousing "therapeutically optimal alarming stimuli." The adrenal glands of the domesticated Norway rat were found by Richter to have undergone marked atrophy during the process of domestication, and presumably were less able to protect the animal against hazard and stress than were the adrenals of rats that lived in their natural environment of peril. I have quoted in this connection the statement of Marlow: "Oft have I surmised, and finally have I learned that Peril is the chiefest way to happiness."

The emotional problems of the patient with pulmonary emphysema are those of man in general, plus the fact that his breathing difficulties pose a continuous threat to his health and comfort. The factors involved are too complex to warrant even a general statement, but it is nonetheless important to realize that a special problem exists. Any clinician who sees many of these patients is entitled to his own opinion; it is probably true that his notion of what an individual patient should or should not attempt, in his extra-medical life, will be based more on his own psychology than on an unbiased estimate of the organic illness and its limitations. It has been said that an alcoholic is a man who drinks more than his own doctor. I, too, claim no freedom from bias; nonetheless, I cannot end this chapter without expressing my own conviction concerning the pathogenetic influences that may affect the patient with pulmonary emphysema, for better or for worse, in the socio-psychologic field, apart from the control which the physician exercises in terms of medication and prescribed physical procedures.

I am of the belief that a program generally dedicated to physical and mental rest is fraught with hazard! Muscular atrophy, bodily unfitness, and loss of pulmonary reserve are the result of an unwarranted reduction of physical exertion. Increasing tension, anxiety, hyperventilation and perhaps bronchospasm may be the consequences of inadequate provision for mental excitement and emotional release. Institution of measures which have as their purpose an expansion of the life of the patient, as much as may be feasible, is to my mind a proper objective. Too much should not be promised when the disease is well advanced, since the response to treatment often leaves much to be desired. However, in many cases an improvement of respiratory function may take place at a critical

level and the degree of benefit obtained may yield these patients years of useful living. As a result of advances in many fields of medicine that have applications to the patient with early or moderately advanced forms of this disease, a good deal of reversible pathology may be overcome. It is for such a partially restored patient that we should encourage as wide a participation in stimulating activities as his local society and his personality permit, not simply because he deserves to live fully as a human being but also because constricting his activities for the sake of "conserving his energies" leads to psychosomatic disburbances that, in my view, impair respiratory function itself. The heart of the matter is the physician's attitude. The complexity of the effects of exertion and hyperventilation on the physiologic function of the lungs represents a challenge to our best efforts. The factors which govern the decisions faced both by the physician and the patient will be presented in the book now in publication, in the hope that some additional insight will be provided, not for blanket solutions but for progress toward therapy of the individual patient with pulmonary emphysema.

SENILE EMPHYSEMA*

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Most textbooks of medicine recognize senile emphysema as a distinct clinical entity and classify it under the broad heading of pulmonary emphysema. Nevertheless, considerable difference of opinion exists as to whether senile emphysema represents true pathologic alterations in the lung itself, or the structural changes of senescence which may be mistaken for pathologic degeneration. In his original description of emphysema, Laennec did not include senile emphysema and he did not consider the senile lung as a form of emphysema. This view was also taken by Landis who stated, "In the strict sense of the word, this is not a true emphysema at all. . . .it is but one of the atrophic changes commonly met with in the aged."

On the other hand, Rappaport and Mayer consider the essential pathogenesis to be identical in both hypertrophic and senile emphysema, differing mainly in gross appearance. Richards prefers to distinguish between a mild form of senile emphysema representing a normal aging process in which the pulmonary tissues suffer some loss of elasticity and resiliency similar to other tissues, and a pathologic form with "marked loss of elastic tissue, degeneration of alveolar walls and diffuse coalescence of alveolar spaces, producing in extreme cases a typical honeycomb lung." With such differing concepts, it is no wonder that other descriptive terms such as, non-obstructive, postural, atrophic, and "small-lunged" have been used interchangeably with senile emphysema.

ALTERATIONS OCCURRING IN SENESCENCE

Since the problems of old age and disease, although not identical, are oftentimes so intermingled that it becomes impossible to distinguish between the depreciations which occur in the older individual due to senescence and those due to pathologic processes, a review of the changes in the lung and its supporting structures as a result of aging would help to clarify some of the divergent opinions.

The Thorax

Ventilatory efficiency is dependent in part upon the highly integrated activity of the muscles, joints and bony skeleton comprising the thorax. It is apparent that any structural change in the thorax accompanying the aging process could conceivably alter respiratory function. The aged person is typically pictured as

* From Barach, A. L., and Bickerman, H. A.: Pulmonary Emphysema. Baltimore, The Williams & Wilkins Co., to be published, 1956.

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assuming a stooped, bent-over posture. This position has been attributed to a weakening and relaxation of the musculature of the back, together with changes in the vertebral column. As early as the fiftieth year, Vischer found a measurable diminution in body stature due to alterations in the intervertebral cartilages, which grow thinner, smaller and drier.

In considering the bony and cartilaginous elements of the thoracic cage, much emphasis has been placed on changes occurring in the intervertebral discs. Warthin described the typical senile thorax as having a short, sharply curved spinal column with contracted and thinned intervertebral discs; the thorax was barrel-shaped with a wide epigastric angle. More recently, Takahashi and Atsumi, reviewing the changes in thoracic form with age in 9,369 Japanese, noted that the chief cause of "rounding of the thorax" was a decrease in stature, especially in the sitting height, accompanied by senile curvature of the spine. Nascher claimed that the erect posture caused the discs to become compressed, with the greater stress occurring anteriorly in the dorsal spine and resulting in a spread of the posterior borders. This would account for the increased curvature in this region and the production of a kyphotic deformity.

In a comprehensive study, Coventry, Ghormley and Kernohan reviewed the histologic changes in the intervertebral discs occurring at various decades. In the sixth decade, thinning of the disc was apparent in 3 of the 22 specimens. Fibrillation of the ground substance and calcifications in the cartilaginous plate were common. The cartilage cells tended to lose their distinct outline and the nuclei became pyknotic. In the seventh decade, degeneration was extensive in 13 of the 27 cases. Longitudinal bands of fibrous tissue and calcified plaques were evident. In places, the cartilage was replaced by bone. Tears were frequent, with the annulus showing areas of necrosis and hyalinization. These changes were attributed to the excessive "wear and tear" to which the spinal column is inevitably exposed.

The ribs accommodate themselves to the changed articular relations with the spine posteriorly and the ossified costal cartilages anteriorly by becoming flattened at the sides. These structural changes together with the lessened resiliency of the ribs themselves make for the typical senile chest, which is longer anteriorly, foreshortened posteriorly, and flattened at the sides.

Senescent changes in the synovial membranes, capsular ligaments and supporting tissues of the joints may be expected in the thoracic cage, as elsewhere in the body. In upper costal respiration, the mode of articulation of the upper six ribs with the vertebrae results in an upward and forward movement of the anterior chest in inspiration, with relatively little lateral expansion of the ribs. On the other hand, when the ribs enclosing the lower half of the chest are raised in inspiration, there is a wide lateral flare. With a diminution in mobility of the joints between the ribs and vertebrae posteriorly and the sternum anteriorly, the movements of the lower portion of the thorax are especially impaired, thus handicapping the mechanics of respiration.

Wasting and dehydration of the muscles of the chest wall have been described by Thewlis. At times, there may be an actual proliferation of connective tissue

fibers through the muscles bundles, with resulting loss of elasticity. The greatest atrophy appears to take place in the intercostal muscles and diaphragm. As a consequence of this wasting of muscle, the intercostal spaces and the supraclavicular fossae appear more prominent. These changes in the musculature and ligamentous structures of the chest wall are not peculiar to aging alone but are frequently observed in severe malnutrition and certain wasting diseases.

In roentgenologic studies, Evans reported a loss of skeletal mineral content in the older subject, accompanied at times by partial collapse of the vertebral bodies. This causes varying degrees of kyphotic deformity.

The Lungs

The lungs, in their daily exchange of enormous amounts of air with the external environment, are more exposed to the adverse influences of such an environment and hence show the accumulation of pathologic insults in greater degree perhaps than any other organ of the body. It is extremely doubtful if the pathologist in his necropsy material has an opportunity to observe age changes in the lungs per se. Both Nascher and Rolleston indicated that the primary degeneration is one of atrophy, resulting in a diminution in size and weight. Reichinstein recorded an average change in the weight of the right lung from 570 grams in the age group 65 to 85 years to 438 grams between 85 to 90 years. For the left lung, the corresponding figures were 430 grams to 350 grams. It is frequently noted at the autopsy table that the lungs of elderly subjects do not exhibit the prompt collapse observed in the young. Retractility is sluggish and deflation is incomplete. Pathologists are inclined to accept a moderate degree of "alveolar emphysema," particularly of the peripheral portions and expanding edges, as a normal finding in senescence. In Laennec's classic description of the lungs of the aged, he stated, "The caliber of all their vessels seems diminished, the partitions of their air cells become thinner than natural, on which account, their substance rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on opening of the body, they are found to occupy not more than one third of the cavity of the pleura."

Senile deteriorations in the fibrous connective tissue making up the supporting framework of the lungs are represented by a process of dehydration with a reduction in ground substance. In addition, the connective tissue stroma acting as a depository for the countless numbers of minute particles inhaled from the surrounding environment tends to acquire an increased rigidity. Atrophy of the epithelium has been described by Aschoff as involving a wasting of the columnar ciliated epithelium, degeneration of the bronchial glands and loss of sensitivity of the mucous membrane. As a result, the mucus formed in the bronchi and bronchioles is thick and tenacious. Changes in the lymphoid elements add to the over-all decline in flexibility and resiliency. In this connection, both Saxton and Casarett have demonstrated that the lymphoid tissue in the lungs of rats increases with age to the extent that partial obstruction of the bronchial airway is produced, favoring the development of chronic suppuration and emphysema. Although Karsner mentions that senile pulmonary arteriosclerosis is frequent

after the age of fifty and "practically constant after seventy years of age," the changes in the smaller blood vessels are difficult to divorce from alterations in the alveolar walls themselves.

The increase in the amount and density of the fibrous connective tissue and lymphoid elements, with their extension into the "root zone" and along the bronchial tree, could seriously impair the normal elongation and retraction of these structures. The deleterious effect of impaired bronchial movements on pulmonary ventilation is apparent. In addition, Drinker and Warren have shown that the movements of the lung are extremely important in aiding lymph flow, and adequate drainage is interfered with when these movements are crippled.

Physiologic Considerations

Measurements of lung volume by numerous investigators indicate that there is little change up to the age of 50. Kaltreider *et al.*, for example, found that the vital capacity is only slightly decreased from 40 to 50 years, following which there is a more rapid decline. This was confirmed by Arnett and by Miller. In addition, it was noted that those individuals who continued to be active showed less reduction than those retired from work. The residual volume increases with age and constitutes a relatively larger fraction of the total lung capacity. Both Kaltreider *et al.* and Baldwin *et al.* found an increase in the ratio R.V./T.C. from 20 per cent in the third decade of life to 31 per cent in the seventh decade. This is in agreement with data quoted by Gilson and Oldham. The maximum breathing capacity expressed as the largest volume of air voluntarily ventilated per minute also showed a significant decline with aging.

In the study of Darling and associates on the index of intrapulmonary mixing as a measure of effective distribution of tidal air to the alveoli, it was noted that 3 "normal" subjects over 50 years of age were in a transition zone between the normal young adult and the clinically abnormal subjects. These investigators raised the question as to whether the lungs of elderly subjects could be considered entirely "normal" with respect to effective aeration of the pulmonary alveolar spaces. The anatomic dead space has been reported by Comroe *et al.* as being larger for older men.

Although only a small group of apparently healthy subjects over the age of 50 were sampled (11 males and 15 females), Greifenstein *et al.* confirmed and extended many of the changes in respiratory function discussed previously. An increase in the functional residual capacity, with a mean of 41 per cent, for the ratio R.V./T.C. resulted in a smaller degree of alveolar dilution per breath. The reduction of approximately 50 per cent in the maximum breathing capacity which was proportionately greater than the reduction in vital capacity suggested either a decrease in pulmonary elasticity, bronchial obstruction or compliance changes in the thorax. Eleven of the subjects showed abnormal intrapulmonary distribution of inspired gas which could be attributed to non-uniform obstructive processes, regional reduction in pulmonary elasticity coincident with aging, or to changes in the dynamics of thoracic movements. Since no measurements were made of pressure-volume relationships in the lung-thorax system, there is

no information concerning actual changes in pulmonary elasticity. The arterial oxygen saturation, pCO_2 and pH showed no significant differences from the values obtained in normal young adults. These studies indicated that "definite changes may occur in the pattern of alveolar ventilation in older subjects without producing disability and without being associated with any specific disease."

Pathologic Considerations

Chronic bronchitis is perhaps the most common ailment of the aged. Sheldon reports an incidence of 40 per cent in his series of 477 subjects, and Monroe documented 272 cases in his review. Although chronic bronchitis implies an inflammatory process, pathologic descriptions have been somewhat varied. In all probability, the basic defect is an impairment in the self-cleansing properties of the tracheobronchial tree. With the diminished muscle tone, decreased sensitivity to stimuli and slowing of reflex activity so common in the aging process, the inability to produce an effective cough may result in an inadequate elimination of bronchial secretions in the older person and so predispose to chronic infection. Deterioration in the normal ciliary activity may also favor the retention and accumulation of secretions.

In many of the earlier accounts, emphysema accompanying senescence was thought due to an atrophy of the alveolar walls as a result of faulty nutrition. The wasting of alveolar septae permitted the air cells to coalesce, resulting in the so-called "small chest" emphysema in which the thoracic cage was more or less rigid and ventilation was carried on mainly by the diaphragm. The preponderance of opinion regarding pathogenesis favors the one expressed by Kountz and Alexander, who regard senile emphysema as primarily the result of changes in the thoracic spine, particularly of the intervertebral discs. Christie believes that these changes result in dorsal kyphosis with consequent rotation of the ribs, so that the sternum is pushed forward and the chest becomes barrel-shaped. The size of the thoracic cage is enlarged by virtue of this deformity and the lungs, in following the chest wall, become overdistended so that thinning and atrophy of the alveolar septae occur. Figure 1 illustrates the typical kyphotic deformity and the barrel-shaped configuration of the chest in a 78-year-old patient admitted for the treatment of portal cirrhosis of the liver. The lateral and postero-anterior roentgenograms of the chest shown in Figure 2 reveal a marked "bowing" of the thoracic spine with wedging of the bodies of the 4th and 5th dorsal vertebrae. Spur formation and lipping are prominent. The increased A-P diameter is readily apparent on the lateral view. Although there is an increased obliquity of the ribs, with an increase in the inter-rib spaces, the diaphragm does not appear to be depressed and adequate motion may be demonstrated on fluoroscopy.

Macklin and Macklin believe that "internal sclerotic" changes in all elements of the lung parenchyma due to the increased fibrosis limit the normal movements of the tracheobronchial tree, including the lung root. This fibrosis results in part from the aging process and from repetitive infections. The central portions of the lung are particularly hampered in their movements and only the periphery is capable of expanding along with the thoracic cage. The continuous stretching and over-distention of these peripheral alveoli finally causes break-

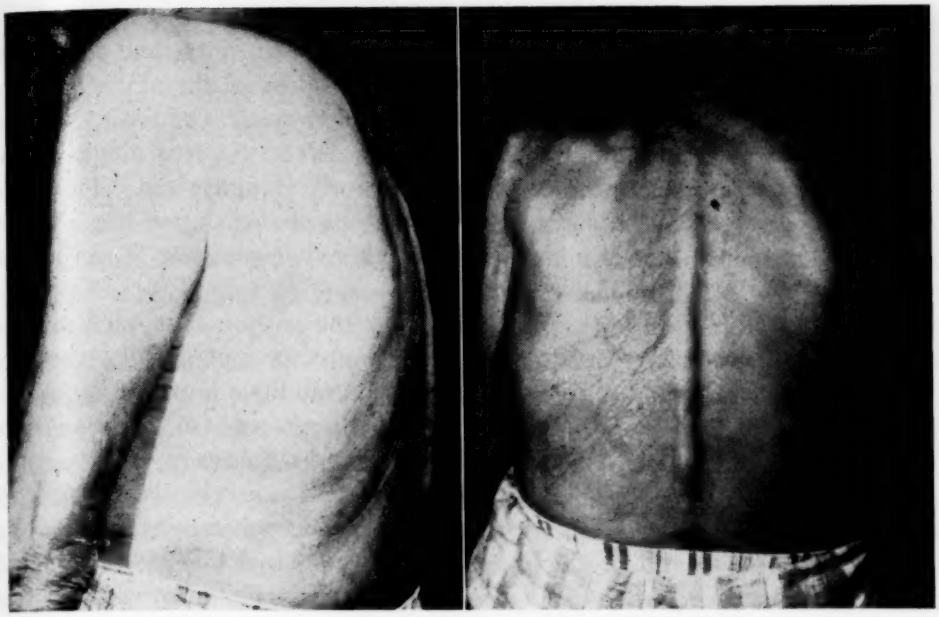

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FIG. 1. Typical kyphotic deformity and barrel-shaped configuration of the chest in a 78-year-old patient.

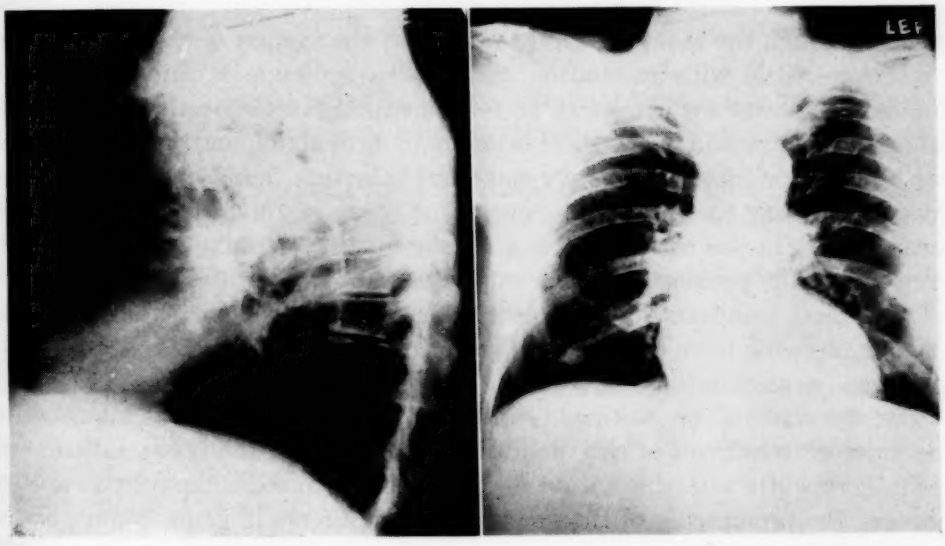

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FIG. 2. Marked "bowing" of the thoracic spine with wedging of the bodies of the 4th and 5th dorsal vertebrae, increased A-P diameter of the chest, spur formation and lipping of the vertebrae, increased obliquity of the ribs and an increase in the inter-rib spaces are illustrated.

down of the alveolar walls. The Macklins also raised the question of a diminished sensitivity in the receptors and afferent pathways initiating the act of expiration in maintaining the chest in the inspiratory state, with a secondary deterioration in pulmonary elasticity. Rappaport and Mayer contend that thoracic changes

lead to senile emphysema in only a minority of the cases. The essential lesion of emphysema at any age is the disappearance of the alveolar septae and progressive coalescence of the air spaces. Functional disuse with loss of "breathing surface" is the main link in the pathogenesis of senile emphysema. "The natural process of involution in the senile lung results in a lung defect which is identical with the developmental and acquired defects of hypertrophic emphysema." The "involutional lung defect" develops into emphysematous changes upon the intervention of the mechanical forces inherent in the labored respiration accompanying dyspnea.

It is the general clinical impression, shared by the author, that senile emphysema is for the most part of little serious significance. In contrast to obstructive emphysema, measurements of pulmonary function are little impaired; nor is the arterial oxygen saturation of the blood significantly altered. On the other hand, Hansen-Pruss and Charlton state that the degree of pulmonary insufficiency is not proportional to the anatomic changes and believe that ventilatory function may deteriorate to a considerable extent. Most of their subjects had evidence of bronchial obstruction and probably represented combinations of hypertrophic and senile emphysema. Franklin, in a recent study on the clinical value of tracings of forced expiration, concurs that many older patients exhibiting thoracic deformities associated with emphysema do not have clinically significant pulmonary disease. Although the vital capacity is reduced, the "expirogram" is normal and no change occurs following the administration of bronchodilator drugs. Although the chest deformity may limit the motion of the thoracic cage, it interferes little with respiration. Since the diaphragm is rarely affected, it retains its capacity for excursion. In fact, breathing in the aged may be largely abdominal in type and unless there is marked loss of abdominal tone, interference with respiratory function is rarely comparable to that found in obstructive emphysema. It may limit physical exertion or be an aggravating factor in other disease states. In this connection, heart disease with congestive failure frequently overshadows the presence of senile emphysema.

The clinical manifestations of these other diseases frequently associated with senile emphysema have occupied the attention of the physician, and have led to widespread neglect in the treatment of this type of emphysema. Since obstructive factors are minimal or lacking, bronchodilator agents are usually ineffective. The vigorous treatment of chronic indolent infections of the bronchial tree with chemotherapeutic and expectorant drugs will be discussed more fully in another chapter. The prompt use of the newer antibiotic agents in acute respiratory infections prevents the further deterioration which accompanies the flare-up of a chronic infection. Although the cough reflex is perhaps the most important mechanism for eliminating retained secretions from the respiratory passageways, the ineffectual paroxysms of dry, hacking cough caused by inflammation of the bronchial mucosa may seriously endanger the life of the elderly debilitated patient. Of special importance for long-term care, the recognition of the necessity for maintaining body tone and physical fitness by a program of exercise designed to improve the mechanics of respiration, has assumed a major role in our therapeutic armamentarium. This will be more fully discussed in the chapter by Dr.

Barach. If "disuse atrophy" plays any part in the pathogenesis of senile emphysema as has been suggested by Rappaport and Mayer, graded respiratory exercises adapted to the exercise tolerance of the patient will result in clinical improvement and will arrest further deteriorations.

SUMMARY

The characteristic features which distinguish senile from hypertrophic emphysema are the absence of bronchial obstruction, a normal or slightly decreased total lung volume, and a slight reduction in compliance consistent with the loss of elasticity in other tissues of the body as a result of the aging process. The primary defect appears to be a structural alteration in the thoracic cage due to degeneration of the intervertebral cartilaginous discs, producing a postural deformity characterized by kyphosis and an increased A-P diameter. Respiratory insufficiency is seldom severe unless complicated by heart failure, superimposition of obstructive emphysema, or associated obesity and hypotonicity of the abdominal musculature (Kerr). Greifenstein and his co-workers, although inclined to disagree with the theory of kyphotic deformity, conclude that "until there is further opportunity for correlating clinical, physiologic, radiologic and pathologic studies in patients of this type, there seems to be little to be gained by using designations such as 'senile,' 'postural'. . .emphysema to characterize pulmonary changes in this group. . . .Lungs 'normal for their age' probably do not have the same reserve as those of young adults."

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THYROID FUNCTION AND DISEASE IN OLD AGE*

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The glands of internal secretion, like other structures of the human body, are variously altered by the passage of time, depending somewhat upon the functions they are expected to serve during the several epochs of life. The thyroid gland is no exception. It plays a considerable role in the growth and development of every organ and tissue of the body, so that it is little wonder that between 15 and 20 years of age it normally achieves its greatest size and probably at this time or shortly thereafter, its maximal function. Changes of a senile nature may be noted at about the age of 40 years; they differ only quantitatively from the more obvious alterations of much later years.

At the present time, we are engaged in a study of the thyroidal function of the inmates of a 2500-bed hospital for chronically sick and aging subjects. More than two-thirds of the patients in this hospital are 65 years of age or older. Aside from the arteriosclerotic changes compatible with age, more than half of these subjects can be regarded as normal individuals. Against this background, we are trying to gather data relative to the size of the thyroid and its functional activity as measured by behavior, basal metabolic rate, radioactive iodine uptake and serum protein-bound iodine determinations. Also included are the incidence and nature of various disease processes, and the relationship between diseases of thyroid and disturbances in other glands, particularly the gonads.

CLINICAL STATUS OF THE THYROID IN PATIENTS WITHOUT RECOGNIZABLE THYROID DISEASE

A. Changes with aging in the size and microscopic appearance of the thyroid

There is a general feeling that between 60 and 80 years of age, the thyroid is reduced in size. This is confirmed in the present study, which thus far includes only data from a representative number of women (Table 1). In 79 per cent of this group, the thyroid was recognizably small or not palpable. Only 13.6 per cent of the women showed a normal sized gland (estimated to be between 20 and 35 grams). Diffusely enlarged and large nodular goiters constituted an additional 7.4 per cent. These gross changes are in keeping with postmortem and experimental histologic findings in both man and laboratory animals. In conjunction with a decreased blood supply, both relatively and absolutely, the interacinar spaces show an increase in hyaline and connective tissue (1–5). There is a decrease in the size of the individual follicles and an atrophy of the follicular epithelium (4, 5)—changes probably secondary to the altered interacinar structures.

* Presented at the Graduate Symposium on Geriatric Medicine, American Geriatrics Society, New York, N. Y., November 30 and December 1, 1955.

TABLE 1

Clinical Condition of the Thyroid in Women Between 65 and 98 Years of Age (Average, 76 Years)

Size of Thyroid	Per Cent of Total Number	Age of Subject (Yrs.)	
		Range	Avge.
Normal	13.6	66–98	80.2
Enlarged—diffuse	2.5	64–79	71.5
Enlarged—nodular	4.9	65–87	75.2
Small—below 15 Gm.	25.9	65–79	73.9
Small—with only one palpable lobe	18.5	66–88	75.0
Not palpable	34.6	65–93	76.6

B. Functional alterations in the thyroid during aging

Our figures for the functional alterations which take place during extreme old age are not final, for some of the subjects have not been checked, and it is desired to have more than one set of data in most of them, if not all, before establishing standards and standard deviations. At present, the results show definite trends in certain of the studies. These alone will be recorded. A considerable mass of data on points not mentioned here will be withheld until the evidence warrants definite deductions about the trend of the observations.

1. *The basal metabolic rate.* In Figure 1 we have compared data from the standard tables of DuBois as modified by Boothby and Sandiford (6) with observations on patients at Bird S. Coler Hospital. For men between the ages of 65 and 69, the number of calories generated per square meter of body surface

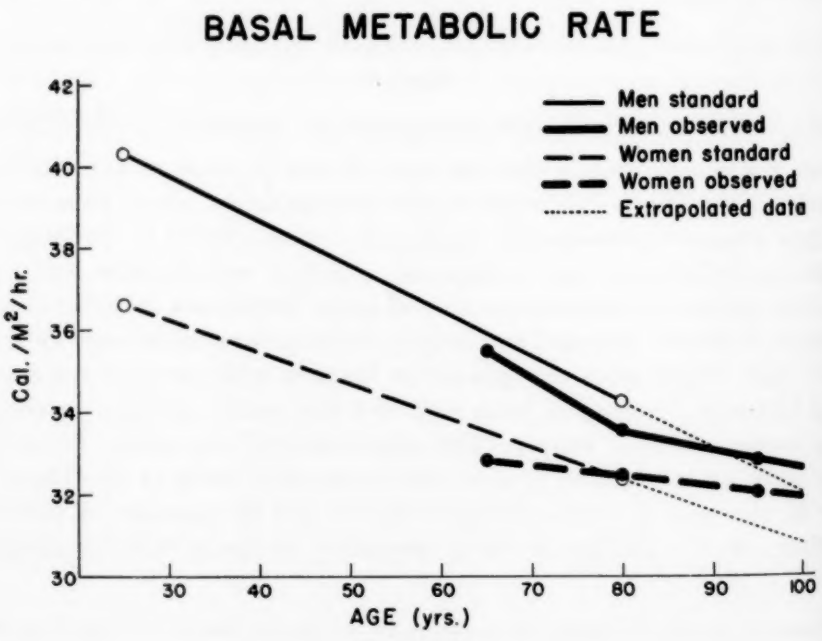

FIGURE 1

per hour was 35.4; between 70 and 74, 34.8; between 75 and 79, 34.0; between 80 and 84, 33.5; and between 85 and 94, 32.8. These values lie close to the standard, but appear to "level off" in extreme old age. The same thing apparently occurs in women, for whom corresponding age values were, respectively, 32.8, 32.4, 32.4, 32.4 and 32.0 calories. Approximately 75 per cent of these values lay within ±10 per cent of the standard values.

2. *Serum cholesterol level.* With the method used for determining serum cholesterol concentration, the total was considered high if above 250 mg. per 100 cc., and low if under 140 mg. per 100 cc. When the small glands and those not palpable or with only one lobe palpable were grouped together, it was found that 54.1 per cent of the subjects showed high values for serum cholesterol concentration, as contrasted with 20.0 per cent of the subjects who had normal and palpably enlarged glands.

3. *Thyroidal radioactive iodine uptake.* A sufficient number of these determinations has not been made to detect a trend. It has been reported that age does not materially influence the percentage uptake of I^{131} by the thyroid (7), but one group of investigators states that the values, although lower than for young adults, do not decrease further beyond the age of 60 years (8).

4. *Serum protein-bound iodine level.* There is a trend towards a gradual decrease in values for both men and women as they reach the seventh, eighth and ninth decades of life, but individual variations are relatively large and we have not yet made enough determinations to warrant statistical analysis. Kountz and his associates observed a decrease for men which was correlated with the diminution in oxygen consumption, whereas no such relationship could be established for women (9).

C. Clinical findings which are often indicative of thyroid dysfunction

1. *Rough, dry skin.* In the subjects with small glands or those in whom the thyroid was not palpable, the skin was found to be rough and dry in 48.0 per cent as compared with approximately 14.2 per cent of those with normal-sized glands.

2. *Coarse hair.* This factor showed no consistent correlation with the basal metabolic rate or the size of the thyroid.

3. *Constipation.* Constipation was complained of by 40 per cent of the subjects with thyroids of normal size and by a slightly lower number of those in whom the gland either could not be palpated or was definitely smaller than the average.

4. *Associated pelvic disease.* In four-fifths of the patients who had had a hysterectomy, there were obvious changes in the size of the thyroid, and in 10 per cent a thyroidectomy had been performed. Further functional data must be analyzed in this group of cases. A previous study was made, in which the incidence of pelvic disease was studied solely in relation to patients seeking relief for a thyroid condition (10). In a series of 467 well-proven cases of thyroid disease, 79.5 per cent of the patients had some disturbance of gonadal function. In 88, or 18.8 per cent, a hysterectomy had been performed for a local pelvic pathologic condition, usually uterine fibroids; in 104, or 22.2 per cent, abnormal menstrua-

tion was observed; and in 180, or 38.5 per cent, some other form of gonadal or gonad-linked pathology had required treatment. The incidence of some form of gonadal involvement in subjects with nontoxic nodular goiter was 86.8 per cent; with toxic nodular goiter, 78.4 per cent; with Graves' disease, 78.0 per cent; with carcinoma, 44.1 per cent; and with hypothyroidism, 88.0 per cent.

DISEASES OF THE THYROID SEEN IN AGING

In our survey at Bird S. Coler Hospital, we have thus far studied disease incidence only in the wards assigned to metabolic and endocrine diseases—a total of 200 beds. Therefore, any figures of incidence of various forms of thyroid diseases will be unduly weighted, particularly as cases of diabetes mellitus represented approximately 50 per cent of the total population. Of the remainder, 3 had hyperthyroidism; 2, spontaneous myxedema; 1, carcinoma of the thyroid; 2, nontoxic diffuse goiter; and 10, nontoxic nodular goiter. Comments on these diseases will be made, not only in the light of experience with the present survey, but against a background of cases seen on other hospital services and in private practice.

1. *Myxedema, and hypothyroidism without myxedema*

Myxedema is more common than usually thought; we were able to collect 65 cases in a general hospital (Metropolitan Hospital) over an eight-year period. The disease presents the same manifestations and runs a similar course, irrespective of the age at onset. That it is more often overlooked or remains unrecognized for a longer period of time in older subjects is apparently due to the ease with which we ascribe many of the manifestations to old age without carefully sifting the evidence. This is even more true in the older patients with hypothyroidism but no myxedema. It is easy to ascribe the weakness, coarseness and dryness of the skin, sensitivity to cold, apathy, impaired memory, sluggish speech and even the edema to the ravages of age. These are the manifestations present in more than 80 per cent of the cases. Even if we add the manifestations which are present in from 50 to 80 per cent of the subjects, the diagnosis will still be missed unless the disease is continuously kept in mind and a basal metabolic rate or some other functional index of thyroidal activity is obtained.

2. *Hyperthyroidism*

The ease with which simple laboratory tests afford us a definite confirmation of the diagnosis of myxedema in the aged is in sharp contrast to the difficulty often encountered in proving the presence of hyperthyroidism among elderly people. Iversen (11) has aptly referred to hyperthyroidism in those over 60 as "a more oligosymptomatic form of the disease" than is observed in the young. Iversen's (11) and Seed and Lindsay's (12) communications, both of which refer to earlier reports, should awaken the clinician to the importance of detecting hyperthyroidism in the aged and the difficulties which such a search entails.

Hyperthyroidism in the elderly should be strongly suspected in the overly alert or hyperkinetic individual, with a nodular goiter and a fast or irregular

pulse with or without signs of cardiac failure. Again, most of the manifestations of the disease in the elderly are similar to those in the young. However, eye signs are usually absent and the severity of other findings may be masked by the diminution of activity normally experienced during aging. Useful in leading us to suspect the diagnosis are:

1. *Continuous* nervous erethism and hyperkinesis at an age when these things are rare.
2. Tremor and warm, moist hands. The coarse tremors not uncommonly associated with cerebral arteriosclerosis may be confusing. However, if these are absent and a fine, rapid tremor is present, this should make one suspect the diagnosis immediately and look for other confirmatory evidence.
3. Precordial hypermotility.
4. A wide pulse pressure. Both No. 3 and No. 4 are not infrequently present in advanced senile decrescent arteriosclerosis or atheromatosis, so that they may be of little help in the individual case.
5. Altered circulation time in the presence of cardiac failure. If hyperthyroidism is also present, the circulation time is not as slow as the cardiac condition might warrant.
6. Loss of weight in the presence of right-sided cardiac failure.
7. Congestive failure resistant to digitalis.
8. Reaction to therapeutic test with antithyroid compounds. These drugs act much more rapidly to improve cardiac failure due to thyrotoxicosis, than to improve such failure due to intrinsic or primary heart disease alone. Moreover, the patient with thyrotoxicosis and heart disease, previously resistant to digitalis, will respond to digitalis once the action of the antithyroid compound is established.
9. A decrease in the serum cholesterol level, an increase in thyroidal radioiodine uptake and an increase in the serum protein-bound iodine level.

3. *Multinodular nontoxic goiter*

This is the most common thyroid lesion in middle and later life. Each patient's problem is subject to the same individualization allowed in similar patients at an earlier age. However, in older individuals there is a greater tendency towards complications which necessitate removal of the gland. These complications include pressure symptoms from a retrotracheal or trachea-encircling goiter, large intrathoracic extensions, or degenerating nodules with hemorrhage and calcium deposition. Large nodular goiters should always be removed, as should any in which one of the foregoing complications is present. A rapidly enlarging goiter should be treated surgically.

4. *Cancer*

In considering the influence of age upon thyroid carcinoma, two points stand out above all others. In the first place, the more highly anaplastic lesions are seen after the age of 40 and diminish considerably in frequency beyond the age of 70 (Fig. 2). Sloan (18) in analyzing 282 cases of all ages, feels that the histo-

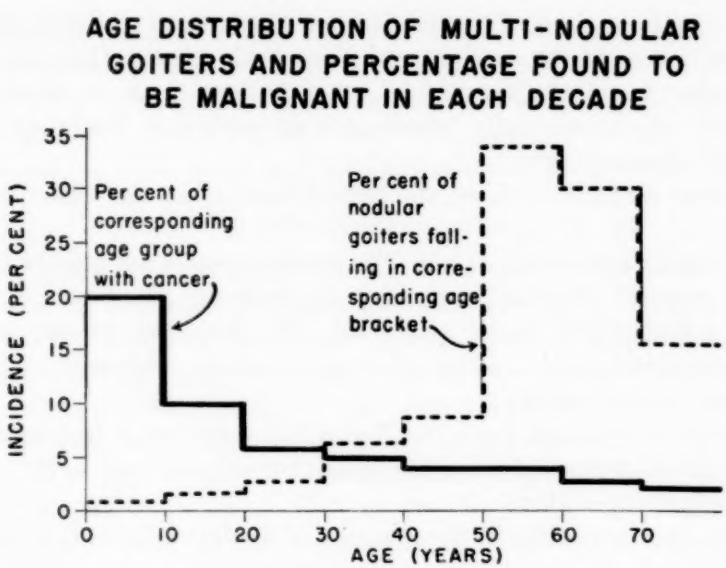

FIGURE 2

logically and clinically more benign lesions occur in childhood and up to the age of 40. The second point is that, although most of the cancers developing in pre-existing nodular goiter occur between the ages of 50 and 70 (Fig. 2), the percentage of such tumors showing malignancy is highest during the first two decades of life.

The curves shown in Figure 2 are derived in small part from our own data and in major part from the combined data of several investigators (13 to 18). Indeed, it is still extremely difficult to obtain material on this subject which derives from a uniform method of collection and classification. Therefore, the actual percentages in this chart must of necessity be approximate, but they show with considerable accuracy the trend of the facts and well illustrate the second point just mentioned.

On the basis of these facts, it would appear that all nodular goiters in patients in the first three decades of life should be removed, whereas from 40 years onward each case should be considered on its individual merits. Certainly there should be no hesitancy in removing all large, encircling and intrathoracic goiters. In the same category is a longstanding nodular goiter recently known to have increased in size. Hardness and nodularity should be another positive indication for thyroidectomy. Pressure symptoms always indicate immediate operation.

Malignancy should be suspected 1) when a nodule appears in the thyroid of a person who has never lived in an endemic goiter area or has no family history of goiter, 2) when pressure symptoms and goiter appear simultaneously, and 3) when a long-quiescent goiter enlarges.

The danger of carcinoma developing in a pre-existing nodular goiter decreases sharply after the age of 70; carcinoma is rarely found beyond the eightieth year of life.

SUMMARY

The thyroid gland in old age is presented from the point of view of the clinical and laboratory findings in persons without recognizable thyroid disease and in persons with various thyroid disorders.

The diagnosis of thyroid disease in the aged is discussed.

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DISCUSSION

Chairman Henderson: This being a graduate symposium, we do not like to think of a discussion period. We would rather have this period one of specific questions. Are there any questions on this paper?

Dr. Daniels (New York): I am very glad to have heard Dr. McGavack. My first question is with regard to the abbreviation ATC. Those letters are quite comprehensible to those who speak about them, but they are not as comprehensible to the rest of us.

Dr. McGavack spoke of precordial hypermotility. Is there any antithyroid therapy other than with drugs, and what drug is used in such cases?

Chairman Henderson: Dr. McGavack.

Dr. McGavack: By ATC, I meant antithyroid compounds. The ones most commonly used are the thiouracils. Propylthiouracil is perhaps the most popular, but methylthiouracil is used almost as frequently. Of the imidazoles, Tapazole is the most popular.

Another preparation, known in Great Britain as Neo-Mercazole and by the generic name carbimazole, is almost equally effective. It has been assumed that this compound is absorbed slightly more slowly and that, therefore, the total dosage may be less. We have not found this to be true and think that it should be used in the same way as the other antithyroid compounds.

These are some of the antithyroid compounds now in use for hyperthyroidism, to which I referred by using the abbreviation ATC.

Precordial hypermotility means that there is a heave to the left chest, which in hyperthyroidism is due to the strong muscular thrust (hyperkinesis) of the heart and the wide pulse pressure. This is related to the tremendous overactivity of the heart in hyperthyroidism and is not seen in all patients. We see it clearly in perhaps a little less than 50 per cent of patients but, when present, it is a useful sign, particularly in younger individuals. In older individuals, it is less useful because the rigidity of the arteries that accompanies senile arteriosclerosis will produce the same type of pulse wave and, therefore, a somewhat similar heave to the left chest.

I think we should not neglect adjunctive therapy. It is well to give attention to digitalis and rest, if this is possible. If the patient is very hungry or undernourished, he should be encouraged to eat more than the average person.

During the time that hyperthyroidism exists and in patients with severe hyperthyroidism, it is important to supply vitamins. The essential ones are the vitamin B complex and vitamin C. Other vitamins will do no harm but are less contributory.

As for specific treatment, all persons with hyperthyroidism should have existing emotional problems solved, as they often precipitate an attack. Particular attention should be paid to the proper indications for therapy with antithyroid compounds, radioactive iodine, and surgery. These three available methods of treatment have specific indications.

MORBIDITY AND MORTALITY IN OLD AGE. A STUDY OF EXPERIENCE IN A MODERN HOME FOR THE AGED. PART I*

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I. INTRODUCTION

In public health, as in most fields, a sure approach to any problem requires full knowledge of the situation to be considered. The plans made and the actions taken are generally only as effective as the body of facts upon which they are based. The problems of the aged—problems that have always been with us—are magnified by the spectacular "aging" of the population; 8 out of every 100 Americans are 65 years of age or older, and the proportion of the aged is expected to increase rather than to decline or become stabilized (1). The problems that have always been most intimately linked with aging and the aged are those relating to disease and death. It is recognized today that the aged constitute the major public health problem of the nation, a problem that is not uniform but varies from group to group. There is not yet, however, a reliable body of information on the nature, incidence and effects of disease among the aged population as a whole, or for any segment of that population.

The health of a community cannot be divorced from the other aspects of living. Health problems are inevitably linked with economic, psychologic and cultural factors. The economic privations that many of our aged endure, the sub-standard dwellings that they must accept, the demoralization that they must suffer as they are forced out of active productive life into frequently unwanted retirement—these, and other such problems make up the general life situation facing the aged. The medical aspects of aging must be seen in relation to this larger setting, for the physical aspects of aging are at the root of the problems of the aged. Any contribution, therefore, to the basic medical knowledge of aging must bear ultimately upon the general welfare of the aged.

This study is one step toward the development of a reliable and comprehensive body of data on morbidity and mortality in old age. The data are derived from the medical records of the Home for Aged and Infirm Hebrews of New York. Because of the policy of the medical staff of the Home, these records are kept with remarkable thoroughness and accuracy. They provide a medical history of each resident from the time of entry to the time of departure. The records are based on an initial pre-admission examination, periodic examinations thereafter, and whatever special examinations prove necessary. When

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This study was carried out under the auspices of the Home for Aged and Infirm Hebrews of New York and is based on the medical and social records of this institution.

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death has terminated residence at the Home, autopsy records are virtually complete; even when residents have left or been transferred for other reasons, it has sometimes been possible to obtain further medical data.

It is hoped that this study will spur other investigators to similar studies of aged people. Only in this way will a sufficient body of data be built up so that new and accurate base lines may be established. Such base lines would be of immediate benefit to public health workers and to the several groups of professional workers who deal with the aged—physicians, nurses, psychologists, social workers, and administrators of institutions and services for the aged. Perhaps the results of this study will suggest new procedures, or modifications of old practices, even before other data become available.

II. THE NATURE OF THE PROBLEM

The aging population

Medical progress—effecting a dramatic lowering of the infant mortality rate—and the vast social and economic gains in the past century have resulted in such a huge increase in the number of aged persons and in the ratio of the aged to the total population, that the population may truly be said to have "aged." The proportion of the aged has grown to such an extent, particularly within the past few years, that the problems created by their numbers equal or surpass those problems which formerly kept the aged population in check.

Modern researchers have found that among Neanderthal men only about 5 per cent attained the age of 40 or more, and 40 per cent died before the age of 11 (2). Among the Romans of the first few centuries of the Christian era, the average length of a man's life was no more than 23 years (3); and in the City of Breslau between 1687 and 1691, the mean length of life was 33.5 years (4).

By 1850, the average length of life in the United States had increased to only 40 years. Although the "average length of life" is a poor indicator of "aging," since it is so much affected by the infant mortality rate, the dearth of population and mortality data for the older population leaves no choice but to accept the aforementioned increases in longevity as indicators of change in life span. Expectation of life in the United States is now more than 65 years, and by 1980 it is expected that it will be appreciably more than 70 years for both sexes (5,6,7).

As a result of such factors as the severe curtailment of immigration to this country after the early part of the century, a long decline of the birth rate during the depression years, and the fact that more and more people are living to the ages which few attained before, the proportion of persons 65 years of age or older in the United States jumped from 4 per cent in 1900, to 8 per cent by mid-century, and the number continues to climb at the rate of 1,000 each day (8, 9). Perhaps even more important, however, is the fact that in 1900 about 4.1 per cent of the population of the United States was in the age bracket of 65 years or older, whereas today that figure is doubled (10). Some recent predictions have it that by 1980 one person in every seven will be 65 years of age or older and the total number of such persons will exceed 24,000,000 (11). By

the end of this century, the median age of the nation is expected to be 50 or higher (12).

There are other significant facts, however, which are not reflected by these over-all statistics. Variations are to be found in different communities. The "aging" of the population has not been uniform; the increase in the numbers of the aged has been much more marked in some regions and in certain segments of the population than in others. In New York City, for example, in the decade from 1930 to 1940, the relative increase of the population was 57 per cent greater among the group 65 years of age and older than among the remainder. The comparable ratio of increase for the nation as a whole was only 37 per cent (13). This variation in geographic distribution of the aged is rivaled in significance by the sex differences in those 65 years of age and over; in this group the ratio is 9 men to 10 women (14).

The huge shift in the age make-up of the population presents inescapable social, economic and medical challenges—challenges which vary in kind and degree from group to group and from area to area. Unrealistic concepts of old age and outdated prejuduce against older workers result in severe economic and social difficulties for more and more older persons. Provision of the means to attain adequate shelter and food for the non-institutionalized aged has received attention only in comparatively recent years. The psychologic needs of the aged are yet to receive their full measure of attention. The problems of physical and of mental health among the aged are particularly striking. With the elimination of many acute illnesses as serious menaces, the chronic diseases have assumed greater importance. Elderly persons with chronic ailments occupy a growing proportion of the hospital beds of the nation. With regard to mental illness, a study in New York State listed persons 60 years of age and older as comprising 13 per cent of the population of State mental hospitals in 1915, but 35 per cent in 1949 (15).

The sheer number of the aged, then, compels us to direct increasing attention to their problems; these problems are not new, but magnified, so that they can no longer be ignored or treated lightly.

Development of interest in, and knowledge of the aging process

Today, probing of the aging process is in progress in many institutions throughout the world, and the activities of the investigators are to a large extent coordinated by such relatively new organizations as the American Geriatrics Society (founded in 1942) and the Gerontological Society (founded in 1944). A Gerontological Research Unit has been established as a part of the Public Health Service of the Department of Health, Education and Welfare of the United States. But long before there were clinicians, pathologists, and statisticians who might think of correlating clinical and postmortem findings to investigate the secrets of aging and death, men sought to explain the inevitability of death. The fall of Adam and Eve—man, originally immortal, rendered mortal because of disobedience to God—is a survival of the many

similar tales current among ancient peoples. This sort of sweeping explanation of the necessity for man's death proved to be sufficient for a long while. Our ancestors were keen observers of the external manifestations of aging, as shown in this passage from Ecclesiastes:

> But remember the Creator in the flower of your age, ere evil days
> come on,
> and years approach when you shall say, "I have no joy in them";
> ere the sun grows dark,
> and the light goes from moon and stars,
> and the clouds gather after rain;
> when the twitter of birds is faint,
> and dull the daughters of song,
> when old age fears a height,
> and even a walk has its terrors,
> when his hair is almost white,
> and he drags his limbs along,
> as the spirit flags and fades.
> So man goes to his long, long home
> and mourners pass along the street,
> on the day when the silver cord is snapped,
> and the golden lamp drops broken,
> when the pitcher breaks at the fountain,
> and wheel breaks at the cistern,
> when the dust returns to Earth once more,
> and the spirit to God who gave it,
> Utterly vain—such is the speaker's verdict,
> everything is vain.
>
> Ecclesiastes XII: 1–8
> (Douay-Rheims Version)

On the whole, however, ancient peoples were content to observe the alterations which occurred with increasing age and to develop practical attitudes toward those who survived to the years when physical and mental deterioration became evident.

With the passage of time, curiosity grew concerning the process of aging and dying. The first investigations in this field were distorted by the fact that the prevalence of diseases among the aged was confused with aging. The Romans considered old age itself to be a disease (senectus ipsa est murbus), and their feeling influenced medical writers for many centuries to seek cures for the complaints of senility without seeking the underlying causes (16). Even today, geriatrics (the term coined in 1909 by Dr. Ignatz Nascher to denote the branch of medicine devoted to the diagnosis and treatment of the diseases of the aged) rather than gerontology (the scientific study of the aging process) claims the larger share of attention. Through the past several hundred years, though, a growing concern with fundamentals, an increasing dissociation of the concepts of aging and disease, can be traced.

The reawakening of interest in life and art that characterized the Renaissance was reflected in studies of the aging process. In the course of his remarkable anatomic studies, Leonardo da Vinci (17) noted the changes that occur with age in the blood vessels and viscera, and he wrote of the differences between the young and the old in physical appearance and abilities. One of da Vinci's predecessors, Nicholas Cusanus (18), suggested that measurements of the pulse rate and of the weights of urine and blood would reveal marked differences between the young and old, as well as between the healthy and the sick. Sir Francis Bacon (19), too, found time to consider the problem of aging, and showed the advanced nature of his thought by developing a general theory of the cause of normal old age, which he distinguished from any diseased condition. He ascribed old age to the failure of the reparative powers of the tissues.

In the seventeenth and eighteenth centuries, the fruit of the overthrow of traditional medical thought became more apparent. Adherence to the teachings of Galen was abandoned in favor of the application of the scientific method—the combination of observation, correlation, and experiment. In the seventeenth century, Harvey laid the foundation for modern physiology, and men such as Kepler and Descartes made their contributions to science. In spite of these great strides in basic science, the keen interest in aging and death, as shown by the popularity of these themes for medical dissertations and speeches, resulted chiefly in studies of specific ailments, such as mitral stenosis, aortic insufficiency, and the role of the heart in sudden death. In the eighteenth century, advances were made in pathologic and clinical correlations; scientific surgery took firm root; there were contributions to cardiac pathology, physiology and therapy, and to cerebral physiology. It was in the middle of this century that there appeared Johann von Fischer's "De Senio eiusque gradibus et morbis" (20), the first medical study of old age to break with the prevailing medical pessimism concerning the aged; in this work considerable space was devoted to an attempted differentiation between normal and pathologic aging.

In the early nineteenth century, although attention was still focused on the diseases of the aged and the influence of age upon disease, increased attention was given to the aging process itself. Anatomic studies of the various systems of the body in old age became more frequent. On the basis of his observations, Bichat, the creator of descriptive anatomy, wrote, ". . . . man, who comes to the end of long old age . . . dies little by little; his external functions terminate one after another; all his senses close up successively" (21).

Scientific progress in the nineteenth century—product of an era favoring rebellion against dogmatism, metaphysics and other influences that restricted human thought—became accelerated, especially in France, where realism and materialism prevailed against the idealism of the eighteenth century (22). Largely because of the effect of this great stimulus on men like Bichat and Cruveilhier, and as a result of the wealth of clinical material available to them in such institutions as the Salpêtrière and the Bicêtre, the French physicians, particularly those in Paris, dominated the medical world of the early nineteenth century. The Salpêtrière, in particular, became a great center for work in neurology and psychiatry, but investigations in many fields were pursued at these

institutions. In the field of old age, the work of Prus (23), carried on at the Bicêtre, may be cited. In an effort to prove the value of medical studies of old age, he investigated the pathologic findings in a series of 390 patients and found the causes of death, classified anatomically, to be: respiratory, 149; nervous, 101; circulatory, 64; gastrointestinal, 49; liver and biliary passages, 8; and miscellaneous, 19.

Most of the significant German contributions were not made until after the middle of the nineteenth century. Seiler (24), a German of the early nineteenth century, however, reviewed the knowledge of his day and pointed out some of the radical anatomic modifications that take place with age; he noted that, although most old people die of disease rather than old age, changes due to disease must not be confused with the results of the aging process itself. Canstatt (25), another German, in 1839 expressed a thought similar to that of Bichat when he wrote that "the old man dies off while living." Canstatt pointed out the many problems remaining in the study of old age and set the standard for all future workers in this field.

The early nineteenth century also found Englishmen and Americans, in increasing numbers, contributing to the discussion and investigation of old age. Dr. P. M. Roget (26), of Thesaurus fame, wrote the following: "Spontaneous decay of the body and decline of its powers, invariably attending the lapse of years, arise altogether from causes that are internal and interwoven with the very conditions and laws of its existence, and are but little influenced by external circumstances."

In discussing the aging process, Dr. Benjamin Waterhouse (27) of Cambridge, Massachusetts, noted that "no particular organ suffers, but a gradual and uniform deterioration supervenes." Another early nineteenth century American, Abel Laurance Pierson (28), found that the wearing out of the organs varies with the individual, depending on such factors as the original constitution of the organs, and the occupation, habits and temperament of the individual. In 1847, a few years after Pierson's statement, the first quantitative clinical study of old age to appear in American medical literature reported on the pulse and respiratory rates in the aged. The author, Dr. Caspar Wistar Pennock (29), found the pulse rate of the aged to be much greater than it was then thought to be; the respiratory rate was found to be what was then expected for middle life.

In comparison with the relatively leisurely medical advances of the centuries past, those of the second half of the nineteenth century were made in a headlong rush, and old age benefited greatly.

Brousse (30) described the functional and organic changes of age, and concluded that senile involution, like death, is the result of living and is due to a general and progressive weakening of the nutrition of the tissues. Geist (31), in the first important German contribution since Canstatt to the study of aging, stated: ". . . . the age involution of the human body does not begin in one organ, and from this spread to others. The involution which we recognize as an alteration of metabolism is simultaneous and general . . ." Cohnheim (32)

ascribed senile atrophy to the effects of disease on the tissue and cells, combined with physiologic changes. Balfour and his group (33), as well as Cohnheim, studied the changes that take place in the vascular system. Möbius (34) turned his attention to the narrowing of the pupil and to the progressive weakening of the patellar reflex with age. Magnus-Levy (35), in 1899, established the fall of the basal metabolism that accompanies aging.

Recognition of the great variations in individual aging was particularly notable among the surgeons. Verneuil (36) wrote that in surgery of the aged bad results were due to acquired disease rather than to years themselves. Blum (37) believed that success in surgery was dependent less on age than on the previous state of health, and Paget (38) wrote, "Years, indeed, taken alone are a very fallacious mode of reckoning age." He noted the greater range of variation among the old than among the young in ability to recover from surgery.

The first American approach to the subject from other than a strictly clinical viewpoint was made by Minot (39) at the end of the nineteenth century. He claimed that the rate of growth diminished from birth because of a steady loss of vitality from that point onward. In his studies, he noted alterations in the structure of the cell with aging (40).

Throughout this extremely active period, there were calls for further studies utilizing new approaches. Beneke (41) stressed the need for more anthropometric studies of the different anatomic systems at various periods of life. Jules Boy-Tessier (42) urged that the physician must know a good deal more about the period of senescence leading up to old age, and not merely the already achieved senile involution.

Twentieth century thought has been built on this background. Sir Humphry Davy Rolleston, writing in the Encyclopedia Brittanica (43), attempted to sum up early twentieth century opinion by stating that the more highly differentiated animals, those which cannot avoid death by simply dividing in two, depend for their life upon an inherited physicochemical constitution which, like a clock, is set for a definite period. Some writers (44–47) sum up the matter as follows: Aging, in a sense, begins at conception; in old age the decline is rapid enough to be visible. The alterations of aging occur in the structure and function of every cell and tissue of the body, but the rates of alteration vary among individuals and among the different organs and functions. The cells lose water and pile up useless or poisonous materials which they cannot eliminate; they gradually slow down in their nutritional processes and lose their self-repairing properties. The weakest areas are the cardio-vascular system, the kidneys and the joints.

With regard to the illnesses of old age, contemporary opinion holds that, in ways not yet understood, the aging process seems to make the individual more susceptible to various diseases, since "the reaction against disease in the aged is produced in the same way as in the adult, but is as much enfeebled as the coefficient of vital resistance is diminished" (48). As recognized by earlier workers, however, chronologic age is deceptive. Today, as in the past, it is felt that important clues to the disorders that manifest themselves in the later

years will be found when adequate histories are available of the so-called healthy years from childhood until roughly the age of 50 years, when the first complaints of age may call for medical attention.

The changing status of the aged

The position of the aged in the community varies from culture to culture, and within any given culture it is likely to vary with the time and place and the multitude of conditions affecting community life.

Among certain primitive peoples the rigors of life left little choice but to dispose of the aged and feeble—those who could no longer do their share. Hottentots carried their aged to solitary huts where they were left with scant provisions (49); Bushmen accomplished the same end by leaving their old behind when they moved camp (50). Among some Eskimo tribes, the old, feeling unable to care for themselves, wandered off into the barren wasteland to die; other Eskimo tribes were more direct in putting their aged to death (51). Certain primitive peoples are said to have had great respect for their aged, manifested by the killing and eating of elderly kinsmen. Indeed, among some peoples, death from natural causes was considered a great misfortune.

A hieroglyphic inscription found in an Egyptian book of wisdom written about 2700 B.C. reads, "To be old is evil for people in every respect" (52); but from other sources we learn that the Egyptians had high respect for the aged and strongly desired to attain what was considered the maximum age of 110 years (53). Although the older men took an active roll in Greek society and respect for their judgment and wisdom was often manifested, the Greeks, on the whole, prized youth and took a somber view of old age (54). Aristotle, for one, expressed a low opinion of the aged for their many faults, among which he listed garrulousness, indecision and crotchetiness (55). The Romans, on the other hand, had a more favorable view of old age (56). The family and parental authorities were well developed in their society; the Roman senate, the supreme council of state, derived its name from the word for old man. Among the Chinese, the highest esteem has always been reserved for the aged. The Chinese desire to grow old, even to appear old when younger, for age brings about authority. This attitude is expressed in their proverb, "If you wish to succeed, consult three old people" (57).

In the Old Testament (58), there is much evidence of the respected and authoritative position granted to the aged by the ancient Hebrews. Although there are passages like the one in Job (32:16), "It is not always seniors who are sage, or aged men who understand," the predominant tone of the Old Testament is set by the Fifth Commandment, supported by such statements as, "You shall rise up before a man with white hair and honour the person of an old man" (Leviticus, 19:32), and the pleas of the Psalmist, "Cast me not off in my old age, forsake me not when my powers fail" (Psalms, 70:9–10).

The Hebrew philosophy has had a profound influence on Western thought, but there has been, and there continues to be, a struggle between avowed religious attitudes and the attitudes manifested in practice. There seems to be an unsettled rivalry between youth and age.

In speaking of the situation in the United States today, one commentator (59) has said, "Age is not revered as formerly, but is just more or less tolerated." The aged are referred to as "the depository of our wisdom," "our treasure," and "the guardians of our honored traditions"; but, except for the relatively few who qualify as elder statesmen or as leaders in some special field of endeavor, there is often little dignity allotted to the aged.

Like the Greek, modern society tends to be a youth-worshipping one—one that seems to fear old age. As a result, the tendency is to deny the aged the means and the opportunity to achieve emotional satisfaction, economic security, and even physical well-being (60). Certain seemingly outdated taboos are still widely in evidence. Many still express the conviction that it is silly for older people to dance, skate, fly, or wear bright clothes. More important, the young tend to regard the marriage of old people as somewhat ridiculous. In general, persons in their seventies and eighties are relegated to the sideline, although they may be able to function at 80 per cent of the efficiency of their prime (61). In the middle years of life, there is a minimum of "age-grading"; status in these years depends more on talent and social and economic power. Upon entry into life's later years, however, the discovery is quickly made that, as in youth, the judgment of society is determined largely by chronologic age. To the reality of physical age, then, is added the fiction of economic and social age. These attitudes put a heavy burden on those entering upon and living through the later years.

One of the most important and unfortunate results of this pushing aside of the aged is their reduction to an unenviable economic plight. The labor force has aged with the aging population, but the older worker faces a general discrimination that exists, even side-by-side with full employment. The obsolescence of machinery, of technics, and of whole industries, and the replacement of these by the new, tends to shut out the old worker without permitting him to adapt his experience, skills, wisdom and judgment to the new situations. In certain firms, the discrimination has crystallized, so that there is a refusal to hire those over 45 (62).

In 1950, the United States Department of Labor estimated that a retired elderly couple needed between $1700 and $1800 per year for a "modest level of living." (This hypothetical couple consisted of a retired husband and wife, both 65 living in a two or three-room flat) (63). Without substantial help, few can attain this standard of living, for it has been found that 30 per cent of the families whose heads are 65 or older have incomes under $1000 a year, and only 15 per cent of families whose heads are 65 or older have incomes of $5000 a year or more. Seventy-five per cent of persons 65 or older living alone (or with nonrelatives) have incomes under $1000 a year (64, 65).

The pressing reality of the situation is reflected in the fact that the aged are the worst housed segment of the population (66). They tend to dwell in low-rent, low-value structures that are dilapidated and deficient in plumbing facilities. They are often housed in places that have been termed "affronts to human dignity." What the low-income families do not want, the indigent aged frequently must take for shelter; and if this is not the case, it is likely that they

are crowded in with married children, with no room to enjoy a normal life. There is little space in city apartments for the idle who must sit at home. These are some of the harsh facts of life which many aged still face.

Development of social responsibility for the aged

Despite the current condition of the aged in our society, the outlook is not bleak. Certainly, although the problems are magnified by the great numbers of elderly people, the present is brighter than the past. The sense of social responsibility for the aged and the infirm has been growing for a long while.

Garrison attributes "the credit of ministering to human suffering on an extended scale" to the teachings of Christianity, and traces the development of institutions for the sick in the Byzantine empire following the conversion of Constantine (67). During the fourth century, specialized hospitals were developed for the aged (gerontrichia), for the sick, for foundlings, for orphans, for the helpless poor, and for poor and infirm pilgrims. During the middle ages, and especially during the Crusades, many local institutions were developed to deal with these functions, singly or in combination; these foundations were generally inspired by the clergy and supported by the nobility. The medieval and Renaissance hospitals, however, were primarily places of refuge for sick strangers and infirm aged individuals without family or friends. There was no organized supervision by physicians. There was a gradual deterioration and breakdown of the monastic charities all over Europe as well as in England, as a result of the changing social conditions and of the increasing interest taken by the municipal authorities in such affairs. Nevertheless, today, the Beguines, a group of lay sisterhoods founded in 1170 by Lambert le Begue, a priest of Liege, are still active, particularly in Belgium. The Beguinage of St. Elizabeth of Ghent has about 1,000 sisters, nearly all elderly women. They devote themselves to a life of service, supporting themselves from the manufacture of fine laces (68, 69).

The past lingered, particularly in America, in still another way. A poor-law enacted in England during the reign of Queen Elizabeth I, authorized the appointment in each parish of overseers of the poor. It imposed on these overseers, and upon the Church wardens, the duty of providing for all classes of the destitute—"able bodies and impotent, children and aged, lame and blind"—and gave them the right to raise funds for this purpose by taxing parish residents. In addition, the courts were empowered to jail anyone refusing to work or to pay the so-called poor-rate. The poor-law, enacted in 1597–98, became part of the English common law which was carried across the ocean to the new American colonies. Until recently this remained the basis of the activities of our local governments on behalf of the poor (70).

In time, the hospital became the center for active treatment of the sick, but in France and Germany homes for the aged also assumed important functions as centers of medical study and research. Two excellent examples of this were the Salpêtrière and Bicêtre in Paris—the former a refuge for aged, chronically ill, insane and even criminal women; the latter a similar institution for men.

Other such institutions throughout France and Germany provided similar opportunities.

In the nineteenth century, the attention of religious and philanthropic organizations began to turn with increasing frequency to the problems of the aged in the community. In the first half of that century, Christian and Jewish organizations began the establishment in the United States of institutions for the care of the aged. Today, there are from 1,400 to 1,500 such institutions in the nation, with some 100,000 residents and a staff of about 9,000. In New York City, as of September 1950, there were over 10,000 persons in such homes, of whom over 1,500, or 15 per cent, received old age assistance checks (71). Such sectarian homes for the aged in many cases charge an admission fee which covers the care of the resident for life. There has been a growth, too, of publicly supported homes for the aged; often these have developed from the old county almshouse which is gradually disappearing as the result of enlightened public thinking and the passage of the Federal Social Security Act. One other institution for the aged is the so-called nursing home, generally operated for the profit of the proprietor. Before the enactment of legislation designed to raise the general standards of these institutions, many nursing homes were strongly criticized for the generally poor quality of the service they rendered; many still afford service of the same poor quality. In addition to the publicly and privately supported homes for the aged and the proprietary nursing homes, there are such newer developments for the care of the able-bodies aged as old-age hostels (initiated in England by the Friends), cooperative residences, cooperative boarding homes, and cooperative communities (72).

When, after the turn of the century, the aging tendency of the population became apparent, it was natural that the first public action should deal with the economics of old age. By 1930, 22 states had set up pension systems for the aged. The depression of the 1930's dramatically pointed up the plight of the older unemployed worker, and the result was the passage of the Federal Social Security Law of 1935. Although the system of old age and survivors insurance is considered to be far from perfect, more than 3 million persons were already drawing benefits under this plan by January 1952 (73). By the end of 1952, more than 7 million persons were receiving funds from some public program for the aged—that is, either the Federal system of old age and survivors insurance, or the older and less adequate state systems of old age insurance, which are gradually being supplanted by the Federal program (74). This number, 7 million, was more than the total number of aged persons in 1930. In recent years, the system of private provision for old age security has also begun a great expansion. By 1952, the number of persons covered by private retirement plans exceeded 10 million. The private plans, however, usually depend on the federal old age and survivors program to contribute the greatest proportion of the retirement income.

Although the passage of the social security law acted to keep more able-bodied aged in the community, nevertheless an increasing number of applications from infirm old persons increased the burdens of homes for the aged. The

homes were assured of a new source of support, however, when it was ruled that old age assistance could be paid to people in private institutions; in addition, individuals who previously could not have afforded the expense were enabled to apply to homes (75).

Much more than the economics of old age is encompassed by the ever-increasing interest in age and the aged. Evidence of this was shown recently when workers in the fields of geriatrics and gerontology were brought together in a National Conference on Aging sponsored by the Federal Security Agency. In addition to purely economic needs, the report of this conference listed such basic needs as the following: 1) the achieving and maintaining of maximum personal effectiveness; 2) the constructive spending of leisure time; 3) the achievement and maintenance of well-integrated social relationships; and 4) the achievement of meaningful and satisfying spiritual values and goals.

An example of the practical effect of this new spirit on the state level is given in a report on gerontologic advances in New York State for the year 1950 (76). Among these advances were: the allocation of special housing for the aged, to be constructed with the physical capacities of the aged in mind; the re-evaluation of hobby products of the aged in order to provide a return for their effort; the utilization of adult education courses, especially those concerning retirement; the expansion of counselling and rehabilitation for the aged; increased local interest in the plight of the aged; expansion of mental health programs for the aged; an awakening to the need to provide opportunities to let the aged help themselves; and the growth of day centers for the aged, and of so-called Golden Age Clubs.

Largely because of the investigations of the aging process that have been pursued for hundreds of years, the idea is gradually being accepted that age should not be considered a matter of strict chronology, but rather a complex of physiologic, social, economic and emotional factors. A greater effort is now being made to spread the companion ideas that, regardless of age, psychologic and emotional needs vary only slightly; among the aged, there is still the need for a place in the community, for a sense of adequacy, and for friends; and these are not the needs of the indigent aged only, but of all aged.

The spread of these views is particularly evident among agencies caring for the aged. Churches and synagogues have added to their programs for the aged, case-work services, boarding house programs, housekeeping services, and medical and nursing care. It is now realized that an isolated home is no longer acceptable as a place where the aging can live comfortably and carry on their contacts with the community and the family. Officials of homes for the aged are coming to understand that the needs of the resident of the home are the same as those of the members of the family unit; they include health, affection, emotional security, education, spiritual development, social contacts, work and creative activity (77). The idea has even been expressed that for some persons, admission to a home for the aged should not be considered final (78); it is held that current methods of mental and physical rehabilitation should make possible the return to the community of some of the aged residents of homes.

Few homes for the aged have facilities to provide for all the needs of their residents. With regard to medical facilities, for instance, there are homes which are equipped to provide only as much care for the sick as might be provided in a private home. Medical care in these is furnished for the individual patient when needed, either by other agencies or by relatives. A second group of homes provides nursing care, dietetic facilities sufficient to meet both ordinary needs and the special needs of diabetics, regular visits by a physician, adequate medical records, periodic physical examination of residents, and some laboratory facilities. A third group of homes provides nursing services by registered graduate nurses, complete dietetic facilities, complete diagnostic and therapeutic facilities and equipment, the services of at least one resident physician, and regular visits from a staff of attending physicians and surgeons (79). In comparison with yesterday's homes for the aged, which were hardly more than boarding houses, the present-day homes, even those least equipped, have turned from the philosophy that suffering is a necessary accompaniment of old age.

The comprehensive aims of the most modern and well equipped homes have been outlined by Dr. Zeman[1], medical director of the Home for Aged and Infirm Hebrews, as follows: Such homes are to house, clothe and feed the residents in healthful and pleasant surroundings; they are to organize activity programs for both education and entertainment; they are to prevent disease and accidents and furnish medical care as required, using when necessary such facilities of the community as general, chronic disease and mental hospitals, and visiting nurse and homemaker services. Beyond this, the home is seen as a center for an active teaching program for physicians, nurses, social workers and the public and, equally important, a center for an active program of medical and social research.

The growth of a feeling of social responsibility for the aged and the ever-increasing scope of activities on their behalf have, in turn, raised a host of questions. All of these questions require investigation before properly oriented programs, meeting community needs, can be planned and put into execution for the benefit of the aged group. Questions particularly pertinent to the medical institutional care of the aged are: 1) What are the causes and possible methods of prevention of dependency? 2) What are the learning capacities of the aged? and 3) What are the attitudes, the eccentricities, the emotional disturbances and the individual variations among the aged?

Perhaps the key need is for more intensive probing of the aging process itself—the physiologic slow-down and deterioration and its mental manifestations. Because illness has always been so intimately associated with old age, much more specific information is needed about the nature and incidence of disease and the relationship of disease to death in the aged.

Status of information concerning morbidity and mortality in old age

Longevity itself has always been fascinating to mankind. The recitations in the Bible of the length of life that various ancient Hebrews are reputed to have attained are an example. It was not until 1662 that this curiosity was channeled

[1] Personal communication.

as a result of a growing need for useful information. At that time, John Graunt (80), in England, compiled the first vital statistics; these proved to be the seed from which grew the statistical tables now expanded and revised continually by public agencies and such private organizations as insurance companies.

Even today, the state of health in the community is determined largely from mortality statistics. There is scarcely any knowledge concerning morbidity in the years between 15 and 45, the age period during which may occur the slow and almost imperceptible onset of the long-term illnesses for which medical attention is sought in the later years. Fully 70 per cent of all cases of chronic illness are believed to occur in persons under 55 (81). In the later years, however, the chronic ailments have definitely made themselves felt in the form of disability and invalidism. The morbidity data are still inadequate. One of the obstacles is the accurate identification of cases of chronic illness; this is complicated because the persistence of these afflictions frequently leads to treatment from several sources. As sources of information concerning morbidity, and especially such information as could be used to establish base lines for public health work on chronic or acute illness, such records as those of hospitals are of relatively little value. Frequently these records are inaccurately kept. When they are kept with reasonable accuracy, they suffer from other faults; the records may cover only a portion of the illnesses in the population or only selected groups; in addition, they often lack such significant information as the size and composition of the population from which the sick persons are drawn. Another failure as a source of morbidity information has been the system of universal reporting, under which physicians are required to report certain categories of disease. Until recently, such records were confined to infections and contagious diseases and to certain occupational diseases. For one reason or another, these reports have been seriously incomplete.

The figures available at present do not furnish detailed knowledge of specific population groups based on exhaustive studies of health and autopsy records over a period of years. At best, the available figures permit only enlightened guesses as to the nature and distribution of the various chronic and acute diseases affecting a given population.

Specific needs in studies of aging and the aged

From the long-range point of view, what is needed is a study of lives rather than merely of diseases. Since life phenomena depend on events that have preceded them, it seems evident that observing, recording, and eventually heeding these precedents should make possible the modification of illness. Several approaches to this problem have been proposed, many of them involving complex planning and long-term observation. However, there is a more immediate task of determining the present status of illness among the aged.

In the opinion of competent authorities (82) the expansion of the population and, more particularly, its age make-up has made geriatrics "public health problem number one." Therefore, there is a pressing need for basic information on the incidence and variety of disease among the aged. There is need, too, for

data on the causes of death at various age levels and among different groups in the older population. Finally, information is needed on the prevalence of physical and mental disabilities among the aged, the varying degrees of such disabilities, and the prospects for rehabilitation.

It is recognized that the best approach to the collection of such information would be through a population survey, an intensive investigation of the health and mortality records of a community, in which the selection of the individuals to be studied does not depend on prior knowledge of the presence or absence of ill health. A survey along these lines was carried out recently in Bristol, England. There, the Bristol Local Medical Committee set out to compile a report on the treatment and care of the elderly chronic sick in Bristol, and ended by reporting (83) on the much more inclusive group comprised of the aged infirm ("frail ambulant"), the acute aged sick, and the healthy old person "whose principal need is to be properly housed."

Another approach would be to study a more restricted sample of the population. This paper reports a study of the medical records of a home for the aged. The information gathered should throw light on the health problems of old age in general and on a particular system of care for the aged.

(*To be continued*)

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PSYCHOLOGIC CORRELATES OF SEX HORMONE REPLACEMENT IN THE AGED: A CRITIQUE

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I. BACKGROUND OF PROBLEM

In recent years the literature of gerontology has abounded with the pros and cons of therapy involving the major sex steroids. Yet neither unanimity of experimental evidence nor concurrence of clinical opinion has characterized the field. The relatively early involution of the gonads in comparison to the other organs of the endocrine system impresses one as suggesting more than a casual correlation between their reduced functioning and the many other structural and functional changes by means of which senescence is identified. Claims for the effects of various therapeutic regimens have covered the entire spectrum from rather hostile opposition through caution and reserve to almost hysterical optimism. Furthermore, partisanship, rather than impartiality, has often been characteristic of evaluative attempts. Indeed, it would not be wise to sample but a single paper and then try to generalize on the basis of the group of papers from which it was drawn.

As Masters stated in a recent article (1), it is up to the advocates of a new type of therapy to demonstrate its merits rather than the responsibility of the skeptics to discredit it. In other words, the correct procedure for appraising any new form of therapy is to assume the validity of the null hypothesis—*i.e.*, that the proposed therapy has no beneficial effects—and then attempt to disprove it. When the therapeutic agent is presumed to have a discrete and specific function to perform, such as lowering of body temperature or destruction of a known bacillus, the justifiability of rejecting the null hypothesis at a given level of confidence is not difficult to demonstrate. However, when the effects of the therapy are believed to be generalized and widespread, affecting simultaneously many organ systems and networks of physiologic functioning, a simple all-or-none acceptance or rejection is seldom feasible. Judgments of the usefulness of steroid therapy are not independent of what is considered acceptable as a criterion of improvement. Changes in the weights of organs, in the number of cell mitoses, in vascularity, in muscle strength, in intelligence and memory, or in reduction of the tendency to hot flashes have all been proposed at one time or other as relevant criteria. Thus experimental attempts to assess the value of a specific form of therapy are confounded by choice of criterion and method of evaluation.

With respect to histologic and physiologic changes resulting from hormone therapy, the evidence in the literature is mostly favorable. Positive changes attendant upon different therapeutic regimens have been reported by Masters and associates (2, 3, 4), Kountz (5), McGavack, Weissberg and Pearson (6),

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Simonson, Kearns and Enzer (7), and others. Likewise, in a series of animal studies Korenchevsky and associates (8, 9) found certain positive changes to accrue from experimental plurihormonal treatment. In a 1951 review of several studies pertaining to hormones and aging, Kirk (10) concluded that there was at hand enough experimental evidence to demonstrate substantial histochemical effects—such as changes in the uterus, elasticity of the skin, and muscular strength—which would be considered desirable from a therapeutic point of view. However, he added the precaution that the unevenness of influence upon the senile organs could conceivably induce harmful ancillary changes overshadowed by the more spectacular benefits.

It is not likely that this preponderance of positive findings could be due entirely to the publication preference given to papers reporting positive results. It is generally understood that questions about the effectiveness of any pharmacologic agent cannot be fully answered unless evidences of "no change" and "change" are given equal opportunity to be displayed. Especially is this true once a bandwagon effect has been created and the issue becomes somewhat clouded by advertisers' claims hinting that another panacea has been found. Perhaps the investigator who finds a specific form of medication to be ineffectual has more inertia and less communicative zeal than his counterpart with positive findings, but otherwise publication selectivity could hardly be an important variable.

Apart from histologic and physiologic studies, there is little evidence regarding the effects of hormone therapy that pertains to the senescent period exclusively. With respect to broad medical and social functions, climacteric as well as postclimacteric subjects have frequently been studied. The advantages and disadvantages of steroid therapy during the climacterium of both men and women have been of vital concern to the practitioner for years. McLaren (11), although presenting few concrete data to support his position, has expressed the conviction that estrogen therapy, though of value, has often been mismanaged and that the vague nervous symptoms so prominent during the menopause do not justify its use. Likewise, Hess, Roth and Kaminsky (12) have expressed the opinion that androgen therapy in men over 50 is not warranted unless there is clear evidence of testicular insufficiency. They feel that the possible dangers of stimulating occult prostatic carcinoma are not balanced by the possible reduction in the vague symptomatology of the male climacteric period. Taylor (13), on the other hand, avers that hormone treatment is the one of choice, even in women with a family or personal history of cancer. The question of possible carcinogenic properties of the estrogen-androgen family is another unresolved issue which is, however, tangential to the present topic.

Despite the widespread interest in the psychologic benefits accruing from hormone therapy, experimental evidence on the subject is meager. Most workers in the field are ultimately concerned with psycho-social changes, even though their immediate research interest might be with different aspects of therapeutic response. The underlying rationale of much research has not been that changes in the sex organs themselves are of any great value to older subjects but that

certain functional by-products of such treatment may be of tremendous value. Furthermore, most clinicians who have advocated the use of steroid therapy have done so on the basis of purported total response of the treated subjects. For example, one can find claimed for sex hormone therapy in older women such improvements as: an increased sense of well-being, more physical strength, energy and endurance, better initiative, improved sexual response, more optimism, and other psychosomatic correlates such as a reduction in the number of disturbing physical symptoms.

The paucity of concrete data with which to back up such claims does not mean that they are entirely unwarranted, for the dearth of experimental evidence is counterbalanced somewhat by a wealth of clinical observations which have been shared in the literature. Although no one would deny the relevance of such observations for suggesting new hypotheses, seldom in clinical work can there be sufficient objectivity and control of conditions to permit data so gathered to substitute for experimental proof.

II. EXPERIMENTAL STUDIES

As stated earlier, any attempt to assess the effects of hormone therapy is confounded by the choice of criterion. When psychologic changes are being investigated, psychologic tests generally provide criterion data. Some of the difficulties inherent in the use of psychologic tests with an aged population have been discussed by the author elsewhere (14, 15). Nevertheless, such instruments compensate for lack of sensitivity with an increase in objectivity, and objectivity is a prime requisite in such evaluations.

One of the earliest studies using performance in psychologic tests as a criterion of improvement was that by Vernon and McKinlay (16). They investigated the effects of vitamin and hormone therapy on senile men. Seventy senile patients were examined with an extensive series of tests; 40 were then treated with vitamins B and C and methyltestosterone and the remaining 30 served as controls. There was no general improvement in intellectual efficiency or psychomotor performance. In severely deteriorated subjects there was some improvement in the performance of certain intellectual tasks and, in more intact subjects, some increase in fluency following the vitamin treatment. The hormone treatment was quite ineffectual. However, it should be noted that the testosterone treatment was given for only four weeks, the psychologic re-test being made after the third week. It would be surprising if any therapy could effect major changes in the area of intellectual functioning in so short a time, except perhaps in subjects very much out of contact at the time of the first testing.

Patients

In recent years a series of studies conducted at the Washington University School of Medicine has involved the investigation of the psychologic correlates of sex hormone therapy in aged subjects (primarily women).[1] The studies first

[1] These studies were stimulated by and carried out in conjunction with the work of Kountz (5), Masters and Allen (2) and others of the Division of Gerontology and the Department of Obstetrics and Gynecology. All projects were financed by grants from the Urbauer Foundation, St. Louis, Missouri.

reported were those of Caldwell and Watson (14, 17) and Caldwell (18). As the details of experimental procedure and results of these investigations have been published elsewhere, presentation here will be somewhat brief.

The behavior of 30 postmenopausal women (mean age 75 years) was sampled by means of a group of psychologic tests (14), chosen to cover the broad areas of intelligence and memory, speed and flexibility of reaction, and important attitudes and interests of the subjects. Selection of tests was guided by consideration of those states of psychologic function often shown to be associated with advancing age (*e.g.*, loss of memory, slowing down of reaction time, and increased rigidity of thought and behavior)—not necessarily irreversible and conceivably susceptible to change as a result of successful therapy.

Following the initial test of all subjects, the women were divided into experimental (hormone) and control (placebo) groups. Unfortunately, from the standpoint of investigating psychologic changes, matching of subjects in the two groups was not precise. In general the experimental group performed initially at a lower level than did the control group. Also the experimental subjects were slightly older, averaging 76 years as compared to 74 for the control subjects. This uneven matching resulted from the necessity in such an experiment of giving priority to gynecologic factors. Designation of the group to which each subject was assigned was carried out without the knowledge of the examiner.

Medication

The experimental subjects were given as basic medication 2 mg. of estradiol benzoate per week intramuscularly and, for the first six months, were allowed to experience withdrawal bleeding periodically. The control subjects were given intramuscular injections of sesame oil. In order to counteract the undeniable differentiating effect of bleeding, both control and experimental subjects were told that the therapy sometimes caused bleeding and sometimes did not, but that this had nothing to do with whether it would make them feel better. After six months the therapeutic dosage was changed by the addition of progesterone and testosterone propionate intramuscularly (5 to 10 mg. per week) to the basic medication estradiol benzoate (2 mg. per week). This change was made in order to provide additional endocrinologic data, the results of which have been reported elsewhere (19, 20). During the third phase of the experiment the therapy was again changed to a stable ratio of 2 mg. of estrogen to 20 mg. of testosterone. The addition of testosterone prevented the annoyance (for so it was interpreted by most of the subjects) of monthly bleeding, without interfering with the effects of the estrogens. Despite the variations in additional medication, the basic dosage of 2 mg. of estradiol benzoate per week remained constant throughout, and all subjects stayed for the duration of the project in the group to which they had originally been assigned. That is, there was no switching of patients from one group to another, which would permit subjects to serve as their own controls. Instead, analysis consisted of a comparison of the amount and direction of change shown by the two groups over the total experimental period. Thus, change shown by the experimental group in the interval from initial to subsequent examinations was compared with that shown by the control group. The

significance of the difference between these changes was then analyzed by means of the *t* test.

Results

After six months

Analysis of the results after six months of therapy, at which time the examiner did not know which subjects had received treatment and which were controls, revealed no spectacular changes in scores for any of the tests administered. However, response patterning based on results with the whole group of tests showed that there were many gains of marginal significance in the experimental group. This suggested that a method of combining discrete scores into a composite might reflect more accurately the changes which had occurred. Accordingly, individual measures were grouped into three composites judged to be measures of *intellectual potential*, amount of *flexibility* or *rigidity*, and general *level of motivation*. Analysis of both individual test scores and of the composite measures revealed a fairly consistent picture; the most impressive changes found were in the areas of memory and intellectual functioning and in a more generally adaptive response to the testing situation, *i.e.*, the treated subjects seemed more willing to expend intellectual energy and to be more highly motivated to succeed.

Even when there were no discernible improvements in the performances of the treated subjects, a difference between the groups could often be detected in the lesser degree of decline with advancing age in the experimental subjects. Changes in the affective area—such as mood, general level of optimism, and attitudes about everyday experiences occurring in the hospital—were consistently insignificant. Either there were no changes in the patients in this area of functioning or else the instruments employed in the group of tests were not sensitive enough to detect them. This negative finding was especially interesting in view of the conviction of so many who have used such hormone therapy clinically that affective changes are among the most probable therapeutic benefits to be expected.

After one year

Further comparison of the groups after one year of therapy revealed no striking deviations from the pattern which had suggested itself after six months. In some instances, particularly in the cognitive area, the minimal changes observable at six months were more impressive after a year. In other areas, such as speed and flexibility of reaction, gains apparent at six months had disappeared after a year. Attitude measurements again showed no appreciable change. In no instance was there a significant reversal of the earlier pattern of change; the control subjects continued to show less improvement than the treated subjects.

After eighteen months

The re-examination of 21 of the original 30 subjects after eighteen months of placebo or hormone injections (18) provided an opportunity to assess the stability of the observed changes. Unless the changes in test scores indicated a

changed potential for adjustment to the subjects' daily environment, the scores would be worthless as criteria. Fleeting improvement in the capacities measured in this study would be of little value to the subjects. In general, results of this 18-month analysis showed a continuation of the major changes, but to a lesser extent. This suggested that a ceiling effect had been reached after about a year of therapy and that further treatment could no longer counterbalance the effects of normal aging—at least not in this group of subjects. It should be taken into consideration that the subjects were appreciably older than at the time of the initial examination and were, furthermore, in that portion of the age curve in which large and rapid decrements in a variety of functions are to be expected.

Group versus individual

All the results thus far discussed have been in terms of group means or averages. The average performance of a given group is a meaningful measure and one which is necessary for understanding a set of data. However, the medical practitioner is often less concerned with how a group will respond to a form of therapy than he is in predicting the response of an individual patient. Some information about the range or spread of scores in both the treated and untreated group would thus be helpful. The spread of scores in both groups was wide; some subjects showed striking gains throughout the procedure, whereas others steadily deteriorated. In general, the dispersion of gains and losses in the control subjects was more negative than positive, whereas in the treated subjects there was generally a preponderance of positive changes. Nevertheless, despite these group trends, the results demonstrated that for an individual subject there may be a decrement rather than an increment in performance following prolonged therapy.

Persistence of effects (Wechsler Memory Scale)

One final question which could be approached through this longitudinal research design dealt with the persistence of therapeutic effects after termination of therapy. At the conclusion of the official experimental period, approximately two years after the initial psychologic examination, no attempt was made to control rigidly the ward conditions which had previously assured a stable environment for all subjects. However, most of the patients continued to live in the same ward under hospital conditions not radically different from those prevailing during the project (except for loss of some contact with research nurses and technicians who administered the injections). One year after termination of therapy, 18 of the original subjects were still available and were given one of the tests from the complete group—The Wechsler Memory Scale. A summary of the results from all four administrations of this instrument may be found in Figure 1. The base line of the graph represents the initial performance level of each group, with deflections above this line representing improvement and those below the line signifying a decline. From the graph it may be seen that, over the three-year period, subjects in the placebo group gradually declined in performance on this memory test. Such a gradual decline is exactly what would be expected of subjects with an average age increasing from 74 to 77. The treated

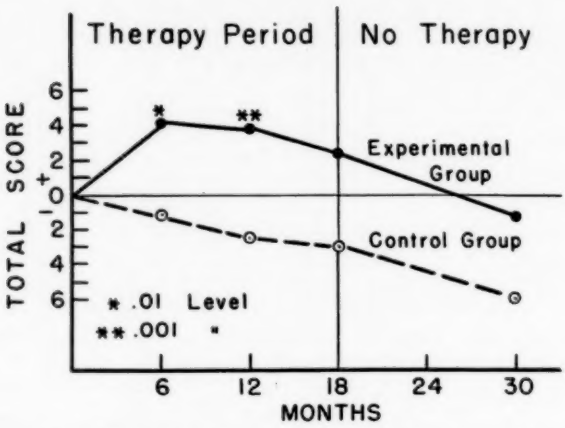

FIG. 1. Changes on the Wechsler Memory Scale in experimental and control groups. (Asterisks indicate statistically significant differences between group changes. The zero line represents the initial performance level of each group.)

subjects, on the other hand, violated the traditional age curve from the first to the third examination. The observed improvement between the initial test and the first re-test was significant at the .01 level of confidence, whereas that between the initial test and the 12-month re-test was significant at the .001 level. The upward deflection observed after eighteen months of therapy, although in the expected direction, was not statistically significant. On the final evaluation, approximately three years after the first testing, the experimental subjects for the first time showed a decrement rather than a slight upward trend. The reversal of trend with cessation of therapy has certain implications for an understanding of the mechanism of change involved. To quote from an earlier paper ((18), p. 171):

"This suggests that changes attributable to the hormones were not permanent and disappeared upon cessation of the therapy. Such a demonstration of the dependence of measurable changes upon continuance of the therapeutic substance gives clues to the nature of whatever modification actually occurred. That is, following certain types of therapeutic intervention (surgery, psychotherapy, etc.) it is anticipated that the introduced modifications, whether anatomic or psychologic, are conducive to sustaining a different type of adaptive response. From all indications, such is not the case with the present type of therapy."

Studies in men

Results from this series of studies, although modest and much more limited than had originally been predicted, were sufficiently encouraging to warrant further investigation in the area of psychologic correlates of hormone therapy. The fact that only female subjects were included in these studies did not mean that benefits from such therapy were presumed to be limited to women. Subsequent studies from the same laboratory have concerned investigations of similar problems with both male and female subjects.[2] Mensh and Mandl investigated

[2] The following experiments were conducted under the immediate supervision of Dr. Ivan N. Mensh of the Division of Medical Psychology, Washington University School of

the relative efficacy of several therapeutic regimens on elderly men. In one phase of this experiment the hypothesis investigated was that improvement in psychologic functioning would be greater in a group of men receiving a controlled low-protein diet plus hormone treatment than would be the case in comparable groups receiving only hormones or a placebo pill. The diet consisted of 1,800 calories daily, with 1 gram of protein per kilogram body weight. Hormone treatment consisted of daily doses of 5 units of protamine zinc insulin subcutaneously and 16 mg. of desiccated thyroid orally. In addition, the subjects were given 25 mg. of testosterone propionate intramuscularly twice a week. The "combined" group received both dietary and hormonal therapy, whereas the "hormone" group ate the regular hospital food. A third, or control group, received no special therapy. At the conclusion of the study there were 8 subjects in the combined group, 5 in the hormone group and 6 controls.

A second phase of the same experiment concerned the ability of the different groups to resist physiologic stress. The stress was induced by daily administration of cortisone acetate followed after three weeks by varying dosages of corticotropin (ACTH). After approximately seven weeks of cortisone and four weeks of corticotropin, therapy was discontinued and all three groups re-evaluated. A comparison of initial test performance with performance immediately prior to induction of physiologic stress provided a test of the relative effectiveness of the various therapeutic regimens, and another comparison of pre-stress performance with performance at the end of the study offered evidence as to the relative ability of the different groups to resist stress, so defined. Criterion measures were included which would sample such traits as manipulatory skill, verbal and visual memory, association fluency, attentional control, willingness to work, and selected attitudes.

A careful analysis of the data failed to confirm either of the initial hypotheses. That is, there were some statistically significant differences among the groups, but no more than would have been expected on the basis of chance. Such differences as emerged at the pre-stress and post-stress testing represented, in the main, those which had existed as a result of inability to secure matched groups in the beginning. In view of the small number of cases in each group, differences would have had to be almost staggering in order to be statistically significant. Furthermore, the design was somewhat vitiated by the presence of 3 patients who had served as subjects in previous diet and hormone studies. Such drawbacks were recognized by the experimenters, but they were unavoidable because of the exigencies of the clinical situation.

Additional studies in women

A second, related study was carried out by Mensh and Mandl, which was essentially a repetition of the earlier Caldwell and Watson study. The subjects were women and estrogen was the basic therapy, with the evaluation period limited to six months. The study differed with respect to certain techniques used

Medicine, and were carried out by Dr. Mary Lyon Sutton and Dr. Billie S. Mandl. Permission to summarize as yet unpublished data has been graciously granted by Dr. Mensh.

in the evaluation, and in the addition of a non-placebo control group. Unfortunately, the groups were again small, with only 6 patients in the experimental group. Furthermore, all these had served as subjects in earlier hormone studies. The results showed more gains of significance in the area of intellectual functioning in the experimental group than would be expected on the basis of chance alone. For the most part, however, the gains followed the same pattern often observed in the earlier work of Caldwell and Watson, *i.e.*, a raising of the post-therapy level of the treated subjects up to the pre-experimental level of the controls. That penalizing of the treatment group (because of uneven matching) should by chance occur twice is unfortunate for interpretation of results. Whereas the study does not deny that change per se is possible as a result of treatment, it does leave unanswered the question of the differential rate of gain that might be shown by two groups carefully matched at the outset.

General

This sketchy review, with perhaps disproportionate attention given to local research, undoubtedly does little to clear the atmosphere of confusion surrounding the question of psychologic correlates of sex hormone treatment in the aged. Some studies have shown benefits related to the therapy which, if not convincing, are at least tantalizing; others have yielded inconclusive if not actually negative results. Experimental methodology has, in general, been commendable, but it has fallen short in several significant respects. Foremost among the flaws has been an inadequate number of subjects to serve as a reliable basis for conclusions. However, perhaps those who have attempted to ignore, if not surmount, the almost ineluctable obstacles in the way of long-term, multidisciplinary research carried on in an institutional setting not always friendly to the aims and ideals of research, can be charitable. Inadequately matched groups and repeated use of the same subjects have further limited definitive interpretation. Finally, the difficulties involved in selection of adequate criteria (which must serve both as a basis for matching of subjects and as indices of improvement) complicate the situation still further. If psychologic tests are to provide acceptable criteria, their functional characteristics (reliability, validity) in aged samples must be better understood.

III. DISCUSSION

These results, although encouraging, lack the consistently favorable tenor of the literature on physiologic changes accruing as the result of sex hormone therapy. How is it possible to explain the observed disparity between physiologic and psychologic changes? The answer must in part lie in the fact that the relationship between internal physiologic changes induced by hormones and external manifestations of change in complex forms of learned behavior is not a simple one. It is unsafe to assume that this relationship is a linear one—certainly not after patterns of previous learning (*i.e.*, habits) have gained priority in determining which of the possible responses in an individual's repertoire will be made.

Another factor which must be considered in answering this question is the

influence of the external environment on the behavior studied. All the research was conducted in institutional settings where environmental stimulants to different activities were virtually nil. The use of controlled settings was essential in order to avoid any effects of differential environmental opportunities on the performance of the control and experimental groups, or, for that matter, on the part of individual subjects within the two groups. Yet this very control, although offering additional experimental rigor, could conceivably penalize the experimental subjects more than the control subjects, as the formation of new stimulus-response connections (*i.e.*, new learning) depends in part on exposure to new stimuli and in part on the opportunity or ability to execute new responses. Within the rather barren environment in which these experiments were conducted, few if any new stimulating conditions which invited different patterns of response, impinged upon the treated subjects. Therefore, at least the stimulus side of the learning paradigm remained unchanged, even though there may have developed as a result of therapy a potential for a changed pattern of response. This is tantamount to setting up an experiment to test the effects of hormone administration upon diet selection and then exposing the subjects to the same bill of fare day after day.

The precise mechanisms of hormonal action are still not known. Beach (21) suggests that hormones may act upon the organism as a whole, upon specific structures involved in different response patterns, upon peripheral receptor mechanisms, or upon the integrative functions of the central nervous system. The last explanation is probably the one favored by most investigators in the field, *i.e.*, that any improvement resulting from hormone administration is probably due to effects of the hormones upon the total functioning of the central nervous system. At different periods of life, such effects upon the nervous system may vary considerably. During the developmental stage, various hormone secretions are essential for any sort of progress. During the latter phases of life, when regeneration and development of new nervous tissue is minimal, hormonal effects upon the nervous system, if any, probably consist of an increase in sensitivity to stimulation. If this be the correct explanation, a question which can be answered only by further research, then once again the importance of an adequately stimulative environment becomes apparent. Such a lowering of the threshold of response does not imply ability to respond at *any* level or to any stimulus; there must still be present a certain critical level and type of stimulation.

This interpretation of the mechanism by means of which psychologic benefits may accrue from sex hormone administration warrants referring again to the necessity of a receptive environment if any meaningful changes are to occur. If we think of the most basic change as a lowering of the threshold for reaction, then we are not likely to lose sight of the fact that there must always be a reaction *to* something. If it is hypothesized that the fund of information will increase, there must be exposure to an environmental field proffering new items of information to be acquired; if attitudes are to change, there must be a social setting in which different nuances of behavior can be expressed and thus perceived.

This interpretation helps to check the tendency to anticipate autogenously determined miracles—new levels of intellectual sophistication, and sudden abandonment of long-cherished stereotypes and reaction patterns. It also places in proper perspective the interplay between the individual (even the elderly one residing in a community home for the aged) and the physical and social environment of which he is a part.

IV. CONCLUSIONS

Despite the impressive psychologic benefits for geriatric patients postulated to occur as a result of hormone therapy, experimental evidence is meager and contradictory. In the studies with positive results, changes are for the most part restricted to the cognitive area and have so far been demonstrated only in female subjects. Furthermore, the carry-over into daily living remains to be established. Improvements in subjective feelings and attitudes, most frequently ascribed to such therapy, have not been demonstrated.

Further experimental investigations of effects of hormone therapy upon psychologic and social functioning in aged individuals are sorely needed before reliable conclusions can be drawn. Also a clear-cut rationale for such therapy should be formulated. Such research with aged subjects can serve a dual function. First, there is the possibility of establishing firmly a therapeutic regimen which would benefit older people in areas in which the effects of aging are often most troublesome. Second, careful investigation of the therapeutic response of older subjects can yield important information for basic endocrinology. Perhaps when more basic facts are known, it will be easier to fit psychologic changes into a meaningful pattern.

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PANEL DISCUSSION ON RHEUMATIC DISEASES*

Moderator†: WALTER BAUER, M. D.

Panelists†: RALPH H. BOOTS, M.D.; RUSSELL L. CECIL, M.D.; RICHARD H. FREYBERG, M.D.; JOSEPH LEE HOLLANDER, M.D.; WILLIAM H. KAMMERER, M.D.; AND CHARLES RAGAN, M.D.

MODERATOR BAUER: In treating elderly patients with articular disease, it is extremely important to realize that, although certain rheumatic diseases are rare in the aged, they nevertheless occur. Thus, rheumatic fever may appear for the first time in an elderly person. The same is true of rheumatoid arthritis. I am sure that various members of the panel have seen patients with their first attack of rheumatoid arthritis in the seventh, eighth, or ninth decade of life. The articular disease that most commonly afflicts the aged is degenerative joint disease, also known as hypertrophic arthritis or osteoarthritis. Why is this not a good place for us to begin?

Doctor Boots, you must see a fair number of patients with Heberden's nodes. What do you tell these people? They all want to know what the nodes mean and whether they represent the beginning of widespread arthritis with eventual crippling.

DOCTOR BOOTS: This is a form of osteoarthritis occurring in the hands, and I admit considerable ignorance concerning the etiology. I have a partial understanding of degenerative disease of the weight-bearing joints such as the spine, hips, knees and feet. Several years ago, Dr. Bauer studied the aging joint changes in cattle, and showed how a young calf used the knees of its forelegs in getting up from the ground. This constant injury to its knees, after a period of several years, produced an osteoarthritis. Heberden's nodes, however, occur in the distal joints of the fingers and are seen much more frequently in women than in men, beginning a few years before or after the menopause. Occasionally, the

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proximal phalangeal joints are involved. In this form of osteoarthritis, weight-bearing plays no part. There may be a hormonal factor that we do not know; neither do we know why Heberden's nodes occur occasionally in men. Probably the most encouraging news for the patient is that the appearance of Heberden's nodes does not indicate that the generalized osteoarthritis will develop. If there is very little discomfort, no treatment is needed. However, if the condition is painful, the physician may suggest daily alternate hot and cold baths for the fingers, immersing them three minutes in hot water and one minute in cold water, alternately, and repeating this three or four times at a session. Salicylate ointment may be prescribed to rub on the fingers at night, and administration of small dosages of salicylates is of value. The most important thing for the patient is reassurance that this form of arthritis is limited and not at all serious.

MODERATOR BAUER: Thank you, Dr. Boots.

What are your ideas about Heberden's nodes, Dr. Freyberg?

DR. FREYBERG: I agree with Dr. Boots. Factors may be involved that we do not understand. I believe that the nodes are not always due to trauma at the distal finger joints. They may occur in relatively young women, and often they are the only manifestations of joint disease until the person becomes 60 years of age or older. Sometimes, other clinical signs of osteoarthritis, never develop although the patients may have had Heberden's nodes since their early thirties. Frequently, there is a history of Heberden's nodes in close female relatives.

The history of these patients' physical activity impresses one with the fact that there is nothing that could be considered excessive physical exertion which would account for injury. Even if this were not the case, why should the nodes develop only at the terminal joints?

I believe two factors, perhaps more, are involved in the etiology of the degenerative changes in the joints, particularly Heberden's nodes: 1) an abnormality, or a difference, in the composition of the cartilages, that may be hereditary, and 2) injury that results from physical activity. Hereditary factors alone may account for the changes that occur early and in persons whose activity has not been excessive.

Whatever the cause, the diagnosis and management are the same. This condition is one that has much current academic interest.

MODERATOR BAUER: Thank you, Dr. Freyberg. I am sure we all agree that Heberden's nodes occur more frequently in women. We have all seen the disease present itself in the twenties in three successive generations, being present in the grandmother, mother, and daughter. Furthermore, Heberden's nodes do occur in women in whom they cannot be ascribed to the wear and tear of work.

Dr. Stecher in Cleveland has good evidence that in the case of Heberden's nodes there is a definite genetic factor. Whether or not this means that these people are born with inferior cartilage, or that some other mechanism is at play, no one can say.

What is the nature of this type of joint disease, Dr. Hollander?

DR. HOLLANDER: A fibrillation and wearing down of cartilage occurs, and is finally complete. An attempt at repair, apparently made at the margins of the

cartilage, the only place where perichondrium remains in the adult, accounts for the bony projections and the development of excess tissue about the joint seen roentgenographically as spurs and fringing.

That this process occurs to some degree in all persons at certain ages is shown in the excellent monograph on aging of the knee joint by Bennett, Waine and Bauer, from which can be learned the normal degeneration at a given age from the standpoint of wear and tear. In certain situations, however, the degenerative process is exaggerated. We do not know with certainty what makes it more pronounced, but it is at least partly due to wear and tear. The wearing down of the cartilage and its final effacement, resulting in an overgrowth of the bone at the joint margin, is the basic change in osteoarthritis.

MODERATOR BAUER: Have you any comments, Dr. Kammerer?

DR. KAMMERER: I think Dr. Hollander covered the subject quite well. Perhaps it is better to describe this disorder as part of the aging process. The question that we should like to have answered is: Why does cartilage in some individuals age faster, or wear out faster, than in others?

Little research has been directed along this line until recent years, but I understand that a group in Boston has considered the possibility that a high-protein diet with protein supplements and the use of crude liver extract may alter an underlying defect in the laying down of protein matrix.

MODERATOR BAUER: The interesting thing about this type of joint disease is that it begins soon after the cartilage reaches full maturity. The earliest changes seen could be due to wear and tear. If this be true, one might ask: Why is gristle or cartilage covering the end of the bone unable to maintain itself? I believe that the answer is not simply a question of wear and tear. We need further information. Until we have better knowledge of the factors concerned in the maintenance of normal cartilage, we shall be at a loss to prevent or control this disease effectively.

Does degenerative joint disease of the spine cause root pain, and if so, what would you say was the treatment, Dr. Freyberg?

DR. FREYBERG: Dr. Bauer, I believe that the terminology may deserve some scrutiny.

Your question, I think, was, "Does degenerative joint disease of the spine cause cervical root pain?" Is that right?

MODERATOR BAUER: Yes.

DR. FREYBERG: I would say "Yes" and "No" to that question, and would clarify this answer as follows:

In most instances, and possibly in all, degenerative joint disease of the spine, whether in the cervical spine or in any other part, does not occur alone.

A better term—one giving a better concept of this whole problem—would be degenerative disease *of the spine*. This would include the posterior facets and the cartilage of the facet joints of the spine that are involved in some individuals. In many instances these joints may be normal or essentially normal, and degenerative changes may involve other structures of the spine—the intervertebral discs and the bodies of vertebrae adjacent to discs that have degenerated.

Degenerative changes seldom involve only the true joints of the cervical spine. More frequently there is a combination of degenerative changes in the intervertebral discs, in the bones about the discs, and around the true joints of the cervical spine.

The pain that results from these degenerative changes includes a root pain due to direct irritation of the cervical nerves as they emerge from the spinal canal. Root pain may be caused by several things: reduction in the size of the foramen through which the root passes, pressure on the root nerve, edema, and swelling around the edges of the foramen.

Many times, pain, not of a full spinal nerve root but of branches of the cervical nerves, may arise from pressure along the branches that pass along the inside of the canal and terminate on portions of the head and neck. Spurs from osteophytes along the posterior portions of the vertebrae may cause such pain.

MODERATOR BAUER: How do you treat these people?

DR. FREYBERG: This is one of the most difficult of the degenerative diseases to treat.

Obviously, the bony and cartilaginous changes are irreversible. Rest alone may help to overcome the soft tissue swellings due to edema and congestion. Many patients are helped by proper positioning in bed, with the spine as nearly straight as possible.

Application of heat may relieve the muscle tightness, but is usually inadequate for relief of nerve root irritation.

Simple analgesics (salicylates) are helpful, but usually do not give complete relief. Narcotics may be required, for short periods only, until other measures have been taken to overcome the changes that cause the pain.

One of the most reliable means of relieving such pain is to reduce the pressure on the nerves by traction, which separates the parts pressing on the nerve. Traction can be applied for long periods comfortably, with the patient in a supine or prone position. The head halter, pulley-weight arrangement, with counter pressure through elevation of the head of the bed, is usually effective. A combination of traction with heat is sometimes more effective.

Patients may obtain a surprising amount of benefit from interval traction accomplished by a Sayre suspension apparatus in a sitting position. Many of these patients can learn to apply this themselves in their homes, but they should be taught by experts in order to avoid accidents.

The proper combination of these measures will usually give great relief, but often the patient cannot be relieved completely and must learn to accept his disease and live with it, being provided the greatest relief possible.

MODERATOR BAUER: Do you have any further comments, Dr. Ragan?

DR. RAGAN: I think Dr. Freyberg has covered it adequately. I believe that radiotherapy does not give much relief in this situation, although it is used as a desperation measure. Salicylates should be used in conjunction with the other measures that Dr. Freyberg described.

DR. CECIL: When these pains are in the lumbar spine, corsets of various kinds are helpful. It is most difficult to induce a woman to wear any sort of brace.

This is a hurdle that every physician who works with orthopedic medicine understands. It is something of a salesman's job to sell a woman the idea of wearing a back support.

MODERATOR BAUER: What is the treatment for degenerative disease of the knees?

DR. RAGAN: Assuming that all we know about such degeneration is the manifestation of wear and tear, an attempt must be made to relieve the wear and tear to the best of our ability. Of course, the usual cause is overweight, so an attempt is made to have the patient lose weight. In acute situations, activity must be restricted in order to rest the joint. If inflammation is present, as is usual in the acute case, an anti-inflammatory agent, such as a salicylate, may be used.

Systemic steroids are seldom advocated. Sometimes, steroids can be injected intra-articularly in acute phases of degenerative joint disease of the knees.

The basic problem should be to relieve the wear and tear as much as possible.

MODERATOR BAUER: Do you agree, Dr. Freyberg? Do you do anything else for these patients?

DR. FREYBERG: The program that Dr. Ragan outlined is fundamentally the most sound. These patients often describe certain activities that tend to aggravate their difficulties. As Dr. Ragan mentioned, wear and tear should be minimized, and I should like to include the avoidance of things that irritate these worn and torn structures.

It is important to analyze the problem in each patient and to put into effect the specific measures that the patient needs.

MODERATOR BAUER: Have you any further comments, Dr. Cecil?

DR. CECIL: Osteoarthritis of the knees is one of the most common problems we have to face. I agree with Dr. Freyberg that occupation plays a large part. I have had several devout patients, for instance, who developed osteoarthritis of the knees from saying their prayers too frequently.

MODERATOR BAUER: Dr. Hollander?

DR. HOLLANDER: I find nothing with which to disagree. The only thing I have to add is that frequently patients with persistent overweight are knock kneed or slightly bowlegged. There is some static deformity—in which case a simple elastic knee cage with side hinges may help to control some of the wear and tear from strains. These patients frequently note that their legs feel unsteady.

We have injected hydrocortisone into osteoarthritic knees repeatedly, as needed, far more frequently than indicated by others. We have been quite pleased with the results, even after five years. No patient has been cured, but by these injections we have helped many patients to carry out their necessary functions in life by making knees less painful.

DR. CECIL: I should like an expression of opinion from members of the panel as to the use of exercises for the knees and the proper balance between exercise and rest. We all know that these patients should have rest and avoid activities that strain the knees, such as standing for long periods or running up and down stairs. However, I suspect that there is a place for regulated knee exercises, not

only for strengthening the knee itself, but for strengthening the muscles and the capsular structures around the knee.

MODERATOR BAUER: You bring up a good point. Many of these patients are benefited by doing quadriceps muscle-setting exercises three or four times a day. They may prevent atrophy of the quadriceps which, if present, further handicaps them. Have you any comments on this point, Dr. Freyberg?

DR. FREYBERG: Yes. It should be emphasized that, if a profile silhouette is made of a typical patient in this group, it is often surprising to see a grotesque looking individual. Dr. Hartung has some interesting pictures made in this way. The patient is usually pot-bellied, has a very heavy trunk, is swaybacked, and has his head and neck thrust forward. There is a tendency toward flexion deformity at the hips, which requires compensatory flexion at the knees. All of this produces strain. You can demonstrate this to yourself, if you stand in such a position for a while. You will find that your knees, quadriceps, other thigh muscles, and calf muscles soon begin to hurt due to the effects of strain.

The purpose of exercises, as Dr. Cecil and Dr. Bauer have pointed out, is to attempt to strengthen parts that move the damaged joints. Articular cartilage and bone are supplied with few or no nerve fibers, and hence damaged cartilage and bone do not directly cause pain; the discomfort arises from the strain on the joint capsule, the muscles, and the ligaments about the joint. If you can improve the static posture and the function of the knees by improving the structures that move them, there will be less discomfort. These patients should always be instructed to do quadriceps-setting exercises and extension exercises for their legs. They should do straight leg raising and the bicycle type of exercises.

No one on this panel is an orthopedist. A question that often comes to mind (and that the patient sometimes asks) is: What help can be gained by surgery?

Relatively little can be done surgically for the patient with characteristic osteoarthritis of the knees. Sometimes, degenerative changes involve the patellofemoral joint more than the femoral-tibial articulation. In some persons, movement of the patella during extension and flexion of the knee causes a great deal of irritation and pain, and stiffness may develop from poor movement. In this situation, partial patellectomy, with removal of the rough, damaged articular surface of the patella, may be helpful.

MODERATOR BAUER: Do you think that patients with loose cartilages, which cannot be held in place by a simple lace or pull-on type of knee cap, require surgery?

DR. FREYBERG: Yes, indeed; anything contributing to degenerative changes in the knee, that can be corrected by surgery, should be so treated. In the knee, as I mentioned with regard to the spine, it is usually not purely a problem of the joint. All the features of the problem must be analyzed and proper attention directed to each.

MODERATOR BAUER: Dr. Ragan?

DR. RAGAN: We are talking a great deal about degenerative joint disease, but I think we have missed one point. When we discuss degenerative joint disease, we are talking about individuals who complain of symptoms, but the

same changes can be seen in patients who have no symptoms. Dr. James Corocadden has found (from studies before and after operation) that in patients undergoing a surgical menopause after an ovariectomy performed long before the usual time for the menopause, symptoms develop postoperatively which we call degenerative joint disease.

I should like some discussion by the panel in explanation of the observation that only a few people have symptoms although everybody has to a certain degree the changes that we have been discussing.

MODERATOR BAUER: Dr. Cecil?

DR. CECIL: It is certainly true that you often find a patient complaining of pain in only one knee, whereas the x-ray films show the same degenerative process in both knees; in fact, the changes in the knee that is painless may be more advanced than in the one that is giving symptoms.

Years ago, I was much interested in so-called menopausal arthrosis. As Dr. Bauer pointed out, we found that artificial menopause patients were the ones with the sharpest pain. I have, however, no explanation to offer.

MODERATOR BAUER: Dr. Hollander?

DR. HOLLANDER: I have been interested in that particular problem for some time, and I think that Dr. Bauer's monograph, which I should like to refer to again, has the answer. The point is that the change in the cartilage and in the synovium of the joint can give rise to pain; the x-ray film shows only changes that are ancient and are scars, rather than the seat of whatever inflammation or active degeneration there may be.

I think the reason that some patients have symptoms, even though they show little roentgenologic change, is that in the symptomatic joints the degenerative process is going on rather rapidly. For instance, we have noted in patients with pain in the knees, that the temperature in the knee joints was higher than that in the knees of a person who had the same amount of degenerative change but no symptoms.

In other words, there must be some irritation from these roughened degenerative surfaces that is producing reflex inflammation. There is a reason for the symptomatology, based upon the degree of degeneration and its rapidity of progression rather than upon the extent of the changes seen by x-ray examination.

MODERATOR BAUER: We have no true explanation for the situation to which Dr. Ragan calls attention. Careful analysis of the histories reveals that, in many of these patients (surgical menopause), although symptoms are referable either to muscles or joints, signs referable to joints are relatively few. Moreover, the few articular signs were present some months previously—when the patients still had both ovaries.

Don't you think that many of these complaints represent arthalgias rather than true joint disease, Dr. Ragan, and don't you think that some of them are muscular in origin? I presume that some of these people have a lower threshold for pain during this period and that there really is little or no accentuation of the underlying articular changes previously present.

DR. RAGAN: I agree with that completely. The thing I wanted to bring out was that, if we start a program of long-continued management such as Dr. Freyberg described, involving muscle-setting exercises over a period of twenty years, the patients will not carry it out unless they are very compulsive. I would much rather look upon this as an acute episode in a chronic condition and try to control the acute episode.

It is difficult to carry out such a program in treating rheumatoid arthritis, a condition in which we are likely to be faced with sustained disease.

DR. FREYBERG: I agree entirely. I hope I did not imply that these people need to do exercises for the rest of their lives. As Dr. Ragan emphasized, periods of complaint often are restricted to a relatively short time.

MODERATOR BAUER: Dr. Boots, have you any questions or comments?

DR. BOOTS: I have nothing to add.

MODERATOR BAUER: When this form of disease involves the hip, it can be quite painful and incapacitating. How do you feel about the treatment of this type of joint disease when it involves the hip, Dr. Kammerer?

DR. KAMMERER: I certainly agree that degenerative joint disease of the hip, so-called morbus coxae senilis, is the form that poses the greatest threat to the patient's normal activities. It also poses the greatest challenge to the physician as far as treatment is concerned. Appropriate treatment depends upon the severity of the disease, upon whether the involvement is unilateral or bilateral, and upon the socio-economic status of the patient.

There are two components to this problem; one is of pain, and the other is restriction of motion. They do not necessarily correspond. Patients with marked restriction of motion may have very little pain; the converse may be true; or both components may be present.

In the milder case, the best advice that you can give the patient is to avoid undue weight bearing. The patient's occupation and position in life must be considered, but unnecessary stair climbing, prolonged walking, or prolonged standing should be avoided. Combined with the use of salicylates as analgesic agents, such a program will often enable these people to live relatively comfortable lives.

The physician has a great responsibility in trying to instruct these patients and to encourage them to live within the limitations that their condition imposes upon them.

In more severe cases, periods of sustained improvement may often be achieved by the use of bed rest for a period of two or three weeks, perhaps in a hospital where hydrogymnastics or non-weightbearing exercises can be carried out, followed by a period of two or three weeks on crutches. This is worthy of a trial, perhaps before more drastic measures are employed.

Symptomatic relief of satisfactory duration is sometimes obtained by the use of intra-articular injections of one of the adrenocortical steroids. This is perhaps not quite as effective in the hip as it is in the knee, probably because it is more difficult to inject the hip joint than the knee joint. When it is possible to inject the material into the hip joint, there may sometimes be a gratifying

prolonged period of symptomatic improvement. This should not be relied upon as the one method of management; salicylates and the other measures mentioned should be employed.

Then there are the patients for whom conservative measures do not suffice—those with increasing pain and limitation of movement, to the point where they are going to become invalids. In these instances, we frequently have to call upon our orthopedic colleagues for corrective procedures, such as cup arthroplasty or the so-called Judet procedure. These are sometimes effective in restoring better functional capacity.

My own belief is that orthopedic correction should be reserved until all other measures have been exhausted and until the patient is psychologically prepared to accept this procedure, which is one that involves considerable hospitalization and expense. The safest rule is to wait until the patient comes to you and says, "I am ready to accept anything; I can no longer go on in the present state of affairs."

Obturator neurectomy enjoyed a brief period of popularity some years ago, and it is still employed to some extent in an attempt to relieve the painful component of degenerative joint disease of the hip. Our experience with it has not been good, and I believe the procedure is falling into disuse.

MODERATOR BAUER: Dr. Boots, what is your experience in treating this type of joint disease?

DR. BOOTS: This is one of the most appropriate subjects that I could think of for the American Geriatrics Society. Dr. Kammerer calls it morbus coxae senilis or malum coxae senilis. It means the bad hip of the aged.

The treatment can be divided into three stages. The first stage applies to patients who have mild pains, as discussed by Dr. Kammerer.

The only point that he may have left out in regard to treatment is physical therapy. Several years ago, I visited many spas in Europe. I was impressed with the use of mud packs to relieve muscle spasm in patients with osteoarthritis of the hip. Mud packs are not available commercially in this country, but as a substitute we frequently use hot ground flaxseed or oatmeal poultices, or hot packs in the form of a moist hot towel placed over the hip and baked with an infra-red lamp for thirty minutes a day. This does not cure the patient, but I am sure many patients will get some relief if they follow a regimen of having a rest period in the middle of the day or after they get home from work, and using this form of physical therapy. Salicylates are valuable and used in most patients. Butazolidin in moderate dosage may provide considerable relief but should be used with great caution in the elderly patient. When there is severe discomfort, it may be well to try small dosages of prednisone; this is only for the occasional patient, as the routine use of steroid hormones is not indicated. Whenever it is evident that the patient can no longer lead a normal life, operative procedures should be considered. Operations for osteoarthritis of the hip have improved greatly in recent years, and one might be more inclined to recommend operation now than a number of years ago. However, I still would not consider any operative procedure until the patient convinces me that he can stand the pain no longer.

MODERATOR BAUER: I agree with what has been said. Usually, we treat these people conservatively. Treatment consists of things such as have been mentioned. We emphasize the importance of full doses of salicylates, protecting the hip as much as possible by means of crutches and hot baths twice a day. We are very prone to prescribe crutches, because when patients use them correctly, they walk more comfortably. All too frequently, however, they are unwilling to go through life on a pair of crutches, so that there comes a day when they want to know if something further can be done.

At the Massachusetts General Hospital, Dr. Smith-Petersen developed what is known as a vitallium-cup arthroplasty. When used properly, there are unusually good results in the majority of patients, though I am sure that most of the members of the panel will say that this has not been their experience. Whether this means that Dr. Smith-Petersen and those who followed him are more meticulous and insist upon a carefully supervised convalescence, I do not know; but most of the patients that I have seen operated on for this type of joint disease are free of pain and have 50 per cent or more of normal motion.

This is an important subject, and I am sure our audience would like a word from any of you about the operative treatment of this type of joint disease. Will you briefly say what you think about it, Dr. Ragan?

DR. RAGAN: Our results over a follow-up period of more than five years have not been as good as Dr. Smith-Petersen's. I think that, if the patient can spend the time in the hospital and if only one hip is involved, the operation of hip fusion is advisable. The end-result is a painless hip without motion, but one motion-free hip is not too bad. If the patient has bilateral hip involvement, there is no point in even considering the operation.

MODERATOR BAUER: Dr. Hollander?

DR. HOLLANDER: Our results in Philadelphia have not been particularly good. One of our orthopedic surgeons was trained by Smith-Petersen, and he performs the operation very well. Yet the range of motion, and the amount of pain-free motion possible after the operation have been disappointing in more than half the patients that we have followed. Therefore we regard it, as Dr. Kammerer put it, as a last-resort procedure. Failing anything else, we do recommend it, particularly when the patient is desperate.

MODERATOR BAUER: Dr. Freyberg?

DR. FREYBERG: I have some very definite opinions about this problem. The patient who can get along without surgery certainly should, and there is no argument, I am sure, from the patient.

However, when the patient says, "Doctor, something more should be done if it is possible," one considers whether or not surgery is applicable and can be expected to be helpful. The differences in results are in part due to differences in surgical skill, but that alone does not explain the differences in statistical results in groups of cases.

An important factor is the selection of the patient on whom the operation will be performed, and another is the many different circumstances. It is one of the hardest things to decide—whether or not to advise or agree that a patient have a hip arthroplasty. If a patient is beyond the age of 65 or 70 years, and

has ambitions in life that do not require much walking, he should not be operated upon; but for a relatively young individual, with a future that he thinks will require a good deal of walking and weight-bearing, such an operation is often necessary if he is to carry out his ambitions.

In general, the younger the individual, the better the results. Such an operation should only rarely be performed on a person past the age of 65 or 70 years. However, in one who has severe pain and severe restriction of motion, and who is otherwise extremely healthy, operation may be indicated if he wants to be more active than the disabilities allow.

In general, a person with degenerative disease of the hip joint does better after this operation than the patient who has rheumatoid arthritis. In the latter case, one is dealing with a continuous inflammatory process that may alter the result.

This is a big problem, Dr. Bauer. Even with the most careful selection of the patients to be operated upon, there will still be failures, because the surgeon cannot always do certain things needed for good results, due to the nature of the damages in the joint structure.

I agree with Dr. Ragan that fusion of the hip may be the preferable operation in unilateral involvement with degenerative joint disease.

Dr. Boots: May I ask a question? I should like to acquire a little more knowledge from the members of this panel.

If the younger patient had osteoarthritis of one hip and the other hip was free of involvement, would you recommend a fusion operation, or would you recommend a vitallium-cup operation? That is the first question.

The second question is: If a patient had osteoarthritis and severe pain in *both* hips, would you proceed with any operation?

Moderator Bauer: I would advise vitallium-cup arthroplasty in both instances. I would hesitate to fuse the hip of a relatively young person with degenerative joint disease of the hip in consequence of a slipped epiphysis, an old fracture, or some other injury. The patient should first be given the opportunity of obtaining a joint with motion, as well as freedom from pain. If vitallium-cup arthroplasty fails, one can always advise a fusion. I would not want a fusion first.

Dr. Freyberg: I am favorably impressed with the results from vitallium-cup arthroplasty, but some of these patients need to be operated upon a second time, if the cup is not sufficiently deep or is impinging. In fact, I have seen some of them operated upon as many as three times before the objectives were obtained.

Dr. Cecil: I think the audience should know the length of time that a patient is laid up with this operation. It is about eight months, so that if he has the operation performed three times, it takes over two years out of his life.

Moderator Bauer: Such an operation is both time-consuming and expensive. For an operation of this type, the patient is in the hospital for a minimum of six weeks. He should also understand that he will be on crutches for at least a year, and that he may have to use a cane for the rest of his life. It is a serious matter.

DR. KAMMERER: Dr. Bauer, a patient whom I have been following for a number of years in the clinic had bilateral disease. Some ten years ago, he had a fusion on one side, and three or four years later, a cup arthroplasty on the other side. Two or three years ago, since the cup arthroplasty was not particularly successful, the Judet procedure was carried out. He is still coming to the clinic, and I dread to see him walk in. He is unhappy despite all of these procedures.

MODERATOR BAUER: You certainly cannot promise a perfect end-result. I think no one of us would contend that.

Perhaps we should go on. Dr. Ragan, what clinical findings should make a physician suspect the presence of gouty arthritis?

DR. RAGAN: The typical patient with gouty arthritis is a male who has a family history of gout and who has episodes of acute arthritis that sometimes involve the big toe. That was described by Scudamore in the eighteenth century, and I think it holds true at present. The typical picture of the acute gouty joint is acute inflammation with a dusky color. It is well described in Hogarth's prints. If you have a woman with possible gout, the diagnosis is always suspect. You have to prove it.

This is the beginning of acute gout. I don't know whether Dr. Bauer meant chronic gouty arthritis or acute gout.

MODERATOR BAUER: You might tell us about both.

DR. RAGAN: Chronic gouty arthritis is probably the later stages of gout in a certain number of patients. They have actual joint destruction associated with tophaceous deposits of urate crystals. In these patients, the useful clinical sign is the tophus in the ear. This can be incised and the tophaceous material easily identified under a microscope. In my opinion, this establishes the diagnosis of gout.

In acute gout, the disease is usually episodic. By the time the patients see the physician, they have had one or two episodes. The response to therapy is often the only guide to establishing the diagnosis with any degree of certainty.

MODERATOR BAUER: Have you any further comments, Dr. Freyberg?

DR. FREYBERG: I agree with all that Dr. Ragan has said. The establishment of the diagnosis deserves some consideration and comment.

I think all of us would agree that the only proof that the physician can rely upon for the diagnosis of gout is the demonstration of urate deposits, either by crystallography or by chemical test. But the diagnosis can be made with reasonable confidence without the demonstration of a tophus, if a person has a typical history of acute attacks, if the plasma uric acid level is elevated, and if response to a test of treatment with colchicine is good.

I emphasize that an evaluation of the blood uric acid level does not always mean a diagnosis of gout. Other things can cause an elevated uric acid concentration in the blood stream. Also, the absence of such elevation does not eliminate the diagnosis of gout. A finding of hyperuricemia is supportive only when other conditions are present; it strengthens the diagnosis, but is not proof of the disease.

The only dependable specific therapeutic test that I know for gout is a quick

response to colchicine. Other drugs will relieve conditions other than acute gouty arthritis, but if a patient shows a quick response to colchicine administered to the point of toxicity, he usually has gout.

MODERATOR BAUER: Thank you.

What do you consider the best treatment for gouty arthritis, Dr. Cecil?

DR. CECIL: I am still in favor of colchicine. Ordinarily, I would give the colchicine by mouth in 0.5-mg. tablets every two or three hours until diarrhea or some other gastro-intestinal symptom occurs. That is the old-fashioned way of administering colchicine in the treatment of acute gout, and it works in a large percentage of cases.

There are resistant cases in which treatment fails, or in which the patient has such a violent reaction to oral colchicine that other methods must be considered. In such cases, we prefer to give colchicine in small doses intravenously. One or two doses every twenty-four hours will often bring about a quick recovery after the oral method has failed.

I shall not go into other forms of treating acute gout, as that is to be taken up in the next question.

MODERATOR BAUER: Dr. Ragan, or Dr. Hollander?

DR. HOLLANDER: Is the question whether there is any further comment about the treatment of acute attacks?

MODERATOR BAUER: Yes.

DR. HOLLANDER: We have been quite pleased with the response of the acute attack to phenylbutazone. It is a simple method of treatment.

I agree with Dr. Cecil in that we would use colchicine first. In patients resistant to colchicine, we have obtained excellent results with Butazolidin, starting with a dosage of as much as 500 or 600 mg. the first day and then tapering it rapidly.

The response is often dramatic. If the patient tolerates Butazolidin, it is the best all-around drug for gout, because it controls the acute attack and, also, can be used either for interval treatment or as a uricosuric agent. However, it should be employed only if colchicine is not effective in a given individual.

MODERATOR BAUER: Have you any further comment, Dr. Boots?

DR. BOOTS: I agree with Dr. Cecil that the most satisfactory treatment for the acute gouty attack is colchicine. However, there are instances in which the results with colchicine are not as good as expected. In such patients, I have used Butazolidin, ACTH, and prednisone.

No one has mentioned the question of diet. It may be wise to recommend low-purine diets to some of these patients whose attacks seem to be brought on by good living.

MODERATOR BAUER: We were for the time being limiting our discussion to the relief of the acute gouty attack. The important thing to remember is that we should prescribe for it properly, as Dr. Freyberg has emphasized. We should start these patients on $\frac{1}{120}$ grain of colchicine every hour for the first six doses, and then every two hours until they have their first loose bowel movement. Until this occurs, the medication is not discontinued.

Unfortunately, the diarrhea is severe and the patients do not like it. It should

be treated. We advise them to take a teaspoonful of paregoric after each watery bowel movement until the diarrhea is brought under control. Some people experience nausea and vomiting in addition to diarrhea. In these instances, the treatment is anything but pleasant and, some patients say, is worse than the disease itself.

Have you something to add, Dr. Ragan?

DR. RAGAN: Yes, I think the amount of colchicine administered should be limited. In the case of a man in a hospital in New York, diarrhea did not develop, and the patient succumbed after taking about 32 mg. of colchicine. In the rare individual, diarrhea will never develop and, since colchicine is a toxic agent, some limit should be put on its use.

MODERATOR BAUER: If a patient has been constipated for some time, I make it a practice to give him a mild laxative, so that I don't have that handicap.

DR. FREYBERG: There may be improvements in the preparation of colchicine for therapeutic use. An ester of colchicine has been reported to be better tolerated than colchicine alkaloid. Esters may be developed which will be better drugs and more pleasant to take.

MODERATOR BAUER: What regimen should a patient follow between attacks of acute gouty arthritis, Doctor Kammerer?

DR. KAMMERER: That will depend to some extent, of course, upon the physician and upon the frequency of the attacks of gout. I think some basic rules can be laid down. If a patient's attacks occur no more frequently than twice a year, a prophylactic regimen is unnecessary. We have agents now that can terminate the acute attack so effectively that the taking of prophylactic medication over a long period of time for infrequent attacks is difficult for the patient to accept. However, if attacks occur more frequently than twice a year, or chronic gouty arthritis develops, prophylactic measures should be instituted.

Fortunately, we have available today at least one agent that is much more effective as a prophylactic agent than any we had before; that is Benemid. Benemid is an agent that will, when given continuously over a prolonged period of time, often prevent attacks of gout, or at least decrease their frequency. It is administered daily in a dosage varying from 1 to 3 Gm., depending upon the patient and upon his kidney function.

Prior to the advent of Benemid, colchicine was thought by some to have certain prophylactic merit. That is probably correct. If the frequency of the attacks is marked, or if the gouty arthritis is severe, the Benemid medication may be reinforced with administration of colchicine in a dosage of 0.6 mg. daily.

In regard to the old and time-tried means of attempting to prevent gout, newer measures have somewhat supplanted the necessity for strict adherence to diets low in purine and the complete avoidance of alcohol. I was never particularly impressed by the effectiveness of dietary restriction in preventing attacks, probably because my patients did not follow the diet prescribed. Nevertheless, Stettin has demonstrated rather conclusively that the formation of uric acid in the body will continue even though the diet is restricted to carbohydrates.

Alcohol in itself, taken in moderation, probably has no bearing on the produc-

tion of an acute attack of gout. Drunkenness does, as it probably acts as a stress phenomenon in producing the attack. Many patients with gout think that certain types of alcohol are safe for them. They believe they are allergic to such drinks as port wine, but they think that they can safely drink Scotch whisky, or champagne.

MODERATOR BAUER: I have never been convinced that Benemid is a good prophylactic agent. I do think it is a boon to patients with gout, in that it makes possible the control of hyperuricemia and thereby prevents tophus formation. It also causes the absorption of tophi. However, I am not convinced that it reduces the frequency of attacks. What do you think, Dr. Ragan?

DR. RAGAN: I am not convinced, but it would be nice if it would. Talbott in Buffalo believes that, after a year of normal uric acid levels, the chance of frequent attacks of acute gouty arthritis is decreased. It is a difficult thing to prove.

MODERATOR BAUER: Would you agree that the other may be even more important in that it may prevent some of the complications of the disease?

DR. RAGAN: I think that is fairly well established. Benemid is a fine drug, in the sense that it causes few reactions. It does cause some, but not many.

It is by no means universally accepted that a full diet should be given to the patient with chronic gouty arthritis or hyperuricemia. Some physicians say that the purine intake should be restricted. Being one who likes food, I am inclined to believe that most gouty individuals do too, and that they do much better if allowed to eat within reason.

MODERATOR BAUER: There is one question that we ought to ask before we close. Dr. Freyberg, what would you say is the best way of treating a patient with rheumatoid arthritis? This is a disease which occurs in the old as well as in the young.

DR. FREYBERG: Rheumatoid arthritis may occur in all degrees of severity. A large number of patients can be managed on a simple program of conservative treatment. This need not be emphasized here, except to say that this program should *always* be put into force. Many patients will get along with that treatment alone. Other things may be needed because of the severity or progression of the disease. The only substances I know of that can be helpful in suppressing the activity of the disease are gold salts and corticosteroids (or corticotropin).

The choice among these is sometimes difficult. Differences of opinion exist, and I am sure there is no agreement as to the details, but one should appreciate that either of these two special treatments may be wisely chosen. One needs to evaluate the patient, the way the medication would be used and the problems that might arise from it, as well as other factors in selecting the special treatment to be employed.

Of the patients I help to manage, about 15 per cent are treated with gold salts in addition to the basic therapy; some of these patients obtain what we consider to be definitely beneficial results. Another 10 or 15 per cent are treated at different times, sometimes for prolonged periods, with corticosteroids. When the disease is causing more difficulties than the patient and the doctor wish to contend with, and when it appears that the disease will progress to cause great

disability, it is justifiable to use any of the preparations known to have beneficial effects. With *all* of them, there is a calculated risk because all of these therapeutic agents possess actions that we do not want. We must use them wisely in order to minimize the difficulties and to obtain the greatest benefits.

The best corticosteroids, now, are prednisone and prednisolone. With these steroids, sodium retention and potassium deficiency in most instances do not occur, so they can be used in patients in whom cortisone or hydrocortisone cause edema. The smallest amounts of these corticosteroids that will give the desired effect should be used. We should not try for complete suppression of the disease because this would require so much medication that troubles will usually be important. We should be satisfied with less than the full beneficial effect, and we must realize that these are only suppressing agents which will produce benefit only so long as their use is continued. The disease process probably continues, and the *end*-result may be no different than if the medication were not used. However, *while* the disease is progressing, the medication may be very beneficial.

The treatment of patients with deformities and crippling can often be aided by orthopedic measures, some nonoperative, some operative.

The patient's general health should always receive attention in the management program.

CHAIRMAN HENDERSON: We are very grateful to this distinguished panel for their discussion of the one real problem as far as disabling disease in this country is concerned. I think everyone realizes that the rheumatic diseases account for more disablement than do all other diseases combined. We are most appreciative of this discussion and I am sure that we all have learned a great deal.

I should like to thank Dr. Bauer and all the members of the panel for being with us today.

RHEUMATOID ARTHRITIS IN THE ELDERLY

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During the past five years we have been interested in the recognition of rheumatoid arthritis in people over the age of 60. Our awareness of the increased incidence of this disease in the elderly stemmed from complaints referable to the musculo-skeletal system in the form of painful, symmetrical joint swellings, stiffness, and localized joint and muscle tenderness, associated with an increased erythrocyte sedimentation rate in the absence of the usual causes for rapid sedimentation (such as anemia, infections or neoplasms). Further observations disclosed constitutional manifestations such as ease of fatigue, anorexia, loss of weight and low-grade elevation of temperature. Roentgenograms of the involved joints often showed osteoporosis, frequently in excess of what one would expect in the elderly, after disuse, or after the menopause.

This report is concerned with 50 consecutive cases of rheumatoid arthritis in individuals over the age of 60, observed in the Arthritis Clinic of the Beth Israel Hospital since January 1950.

CLINICAL MANIFESTATIONS

There were 29 females and 21 males in this series. This differs from the usual sexual distribution noted in younger rheumatoid arthritic subjects, among whom the ratio of female to male is usually 3 to 1. Thirty-four of the 50 patients were between the ages of 60 and 70; the remainder were between 70 and 80, with the exception of 1, who was 82.

The standards recommended by the American Rheumatism Association were utilized in classifying the severity of the disease process. Forty-six subjects were grouped in stage I or stage II, and the rest were in stage III (Table 1).

Twenty patients were known to have had this disease for less than one year; 26, for one to three years; and 4 for over three years (probably undiagnosed).

In most patients the onset was insidious, with mild to moderate articular pain, swelling, redness, heat, local tenderness and decrease of mobility. In the others the onset was acute, with chills, fever, prostration or other constitutional manifestations and acute articular phenomena. In some, monoarticular involvement was predominant early, and was often migratory in character. Eventually, a symmetrical distribution in the joints was observed. Notwithstanding the type of onset, the disease assumed a chronic course, with remissions and exacerbations, not unlike that seen in the younger individuals. In the cases of longer duration, atrophy of muscles, ankyloses and deformity were the rule. Interference with functional capacity was noted in about a third of this group.

The joints most commonly involved were the metacarpophalangeal and the proximal interphalangeal (Table 2). In 26 patients the initial manifestation was

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TABLE 1
*Severity of Disease**

	No. of Cases
Stage I	22
Stage II	24
Stage III	4
Stage IV	0

* According to the American Rheumatism Association classification.

TABLE 2
Incidence of Joint Involvement

	No. of Cases
Metacarpophalangeal joint	41
Proximal interphalangeal joint	34
Shoulder	26
Knee	16
Wrist	12
Elbow	10
Feet	6
Associated osteoarthritis	41
Elevated serum uric acid level	2

in the shoulder. When the small joints of the hand were concomitantly involved, the clinical picture of the shoulder-hand syndrome was simulated. The high incidence of shoulder involvement with the associated shoulder-hand syndrome has been reported by others (1, 2). It is our contention that many cases of this syndrome are really instances of rheumatoid arthritis.

Evidence of additional degenerative joint disease (osteoarthritis) in the form of Heberden's nodes, or involvement of the hip or knee was found in 41 cases. Two patients also had an elevated level of serum uric acid.

Almost all the patients had an elevated (rapid) erythrocyte sedimentation rate (Table 3), which was often the first clue in evaluating the rheumatic complaints that ultimately conformed to the clinical picture of rheumatoid arthritis. Despite published reports that the mean sedimentation rate increases with age (3), it has been the experience of the author and of others (4) that the erythrocyte sedimentation rate (Westergren method) does not change appreciably with aging. Only a small percentage of our patients had anemia; this

TABLE 3
Laboratory Findings

	No. of Cases
Elevated erythrocyte sedimentation rate (over 20 mm./60 min., Westergren)	48
X-ray evidences of osteoporosis	34
Secondary anemia (hemoglobin less than 10 Gm./100 cc.)	11

is in contrast to the incidence of anemia in the rheumatoid arthritis of younger adults.

In early rheumatoid arthritis in the elderly, roentgenographic changes are almost never entirely diagnostic. In the more advanced cases, changes are observed which are similar to those found in younger subjects with the disease. In both early and advanced arthritis of the elderly, there is an increase in the degree and extent of osteoporosis.

MANAGEMENT

It must be remembered that in the management of rheumatoid arthritis, therapeutic measures will include suppressive or supportive remedies that influence signs or symptoms, or contribute to the functional improvement, without necessarily altering the underlying disease.

Routine general advice was given to all the patients regarding rest, proper diet, supplementary vitamins when indicated, and regular bowel hygiene. Oral salicylates, occasionally combined with antacid or buffering agents, often afforded prompt relief of signs and symptoms. When salicylates were given concomitantly with physiotherapeutic modalities, more lasting benefits were experienced. Orthopedic supports for the prevention of deformities, and corrective exercises were of distinct help.

Phenylbutazone (Butazolidin) was not used because of our previous experience with the high incidence of toxic reactions. A few patients received benefit from treatment with gold salts, but the final results require further clinical study for total evaluation.

When rehabilitation was urgent, particularly with the necessity of earning a livelihood, cortisone or corticotropin (ACTH) was administered. Patients were informed that the relief of symptoms would be temporary and would continue only while receiving the medication. They were told that severe side-effects might contraindicate continuation of these hormones. A satisfactory or partially satisfactory response was obtained with a suboptimal maintenance dosage. If a long-term course was contemplated, cortisone was alternated with corticotropin.

Among elderly patients with rheumatoid arthritis, there is a high incidence of coronary artery and hypertensive disease, and an increased liability to congestive heart failure; therefore the sodium intake must be restricted. Oral potassium and occasional diuretics were often required to offset the consequences of sodium retention.

Since cortisone and corticotropin frequently induce an exaggerated sense of well being, accompanied by increased psychomotor activity, physical exertion should be restricted in the elderly patient who has rheumatoid arthritis with coronary arteriosclerosis (particularly if insufficiency has been previously demonstrated). In view of the high incidence of osteoporosis associated with the use of cortisone or corticotropin, caution must be exercised because of the possibility of compression or pathologic fractures. The elderly patient may exhibit the same type of "withdrawal syndrome" as that seen in the younger individual; it is therefore advisable to reduce the dosage slowly before complete

discontinuation. As older people are susceptible to intercurrent infections, particularly respiratory, it is wise to check them at intervals to adjust the hormone dosage accordingly. It is well documented that these hormones may mask the pattern of an infection.

Recently, prednisone and prednisolone were introduced as effective anti-rheumatic agents (5, 6). Our experience to date, although short-term, indicates that these two preparations[1] may be more suitable than cortisone in the immediate management of the elderly patient with rheumatoid arthritis, for the following reasons: 1) as they are used in small doses, there is less likelihood of salt or water retention, particularly in the presence of arteriosclerotic and/or hypertensive heart disease (5, 6), and 2) they may be more effective than cortisone as anti-inflammatory agents (7). The pattern of the disease may be modified by these newer drugs, so that progression is halted and the patient is thus permitted to pursue gainful employment or to carry on with routine housework.

SUMMARY AND CONCLUSIONS

An investigation of 50 consecutive cases of rheumatoid arthritis in patients over the age of 60 indicates that the initial diagnosis of this disease may be established in the elderly. The clinical course is not unlike that seen in the younger person. However, the incidence of shoulder involvement, at times simulating the shoulder-hand syndrome, is higher; there is less tendency towards anemia, and more roentgenologic evidence of osteoporosis. The erythrocyte sedimentation rate is usually elevated.

In the management of rheumatoid arthritis, salicylates and physiotherapy produce beneficial effects in many of the patients. If cortisone or corticotropin are to be used in the rehabilitation program, there should be careful observation, in view of the danger of precipitating cardiac failure, masking intercurrent infections, or inducing compression fractures. Prednisone and prednisolone may be used in smaller doses than cortisone, with less danger of salt or water retention, and may be more effective than cortisone as anti-inflammatory agents. Further studies are in progress to outline the ideal program in the management of this disease.

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[1] The prednisone and prednisolone used in this study were supplied as Meticorten and Meticortelone, respectively, by Schering Corporation, Bloomfield, N. J.

SEVEN-YEAR OBSERVATIONS ON THE TREATMENT OF ARTHRITIS WITH HESPERIDIN-ASCORBIC ACID

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From a clinical point of view, our initial interest in hesperidin (a flavonone glycoside) combined with ascorbic acid (vitamin C) concerned its effect on the capillary fragility and permeability so frequently manifested in rheumatoid arthritis.

In the daily routine of life every person is plagued with minor injuries to various parts of the body. These injuries, more frequently than not, result in slight bleeding which is unsuspected or is given no attention. These bleedings might well become major hemorrhages should the capillary system develop serious defects as a result of more intense trauma or insults from toxic materials of either bacterial, viral or metabolic origin. Psychic trauma and, very often, drugs are etiologic factors in capillary fragility—a fact important to recognize and consider.

"Pathologic changes in the capillary system," stated Aschoff (1), "are at the bottom of many chronic diseases. No physician should disregard the significance of capillary disturbances, as small and insignificant as they might appear to him. Many chronic diseases, grave and incurable, could be prevented by proper attention to disturbances of the capillary system."

Warter *et al.* (2) reported that capillary fragility and permeability were frequently observed in patients with rheumatoid arthritis, and suggested that bacterial toxins or other toxic agents are etiologic factors in the increased tendency to spontaneous petechiae and ecchymoses.

The physiologically basic lesions in rheumatic fever, according to Epstein and Greenspan (3), are believed to be increased capillary fragility and permeability. Montgomery (4) concluded that "rheumatic fever is a disease of the blood vessels." Manwaring and Boyd (5) stated that "disturbances of the circulation undoubtedly constitute a certain proportion of the underlying pathologic changes evidenced in rheumatic and arthritic changes."

Hypertension is yet another clinical entity in which capillary resistance is important. Griffith and Lindauer (6) stressed that patients showing increased capillary fragility are especially predisposed to apoplexy, retinal hemorrhages and even death.

It is thus established that capillary integrity is essential to health, and is a big factor in the successful treatment of disease. The importance of the capillary

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system is classically presented by Boyd (7): "There is a tendency to pay exclusive attention to the heart and the blood vessels. It is often forgotten that the sole function of the heart, the arteries, and the veins is to maintain an adequate rate of blood flow through the capillaries. It is in the capillaries that the essential business of the circulatory system is carried on."

Zweifach (8) viewed the capillary barrier as being referable to an intercellular substance and also to an adsorbed layer of serum protein. From a functional point of view, the cellular component of the capillary walls seems to be unimportant.

The intercellular cement substance obviously plays a prominent role in the integrity of the capillary system. That ascorbic acid may be the important key to cellular integrity is supported by observations (9) made on the metabolic function of this vitamin in the body. It has been observed (10) that the interendothelial cement provides considerable cover for the endothelial cells facing the capillary lumen, and when this substance is removed, bleeding results. There is considerable evidence (11–13) to support the concept that vitamin C is essential for the proper formation and maintenance of the intercellular cement substance. Wolbach and Bessey (14) pointed out that "the hypothesis that ascorbic acid or a derivative is a part of the collagen cannot be excluded."

Vitamin C avitaminosis has been reported as a possible causative factor in capillary fragility. According to Dalldorf (15), ascorbic acid is an essential nutrient required for the normal deposition and maintenance of intercellular substance. Eddy (16) believes that the so-called 'country rheumatisms' developing at the end of a long winter "were actually hemorrhagic joint conditions produced by vitamin C deficiency."

Warter *et al.* (2) found no correlation between capillary fragility (as determined by the positive cuff-pressure test) and the level of vitamin C in the plasma. These findings confirmed results reported by several other investigators.

Scarborough (17) established that a deficiency of vitamin C is not necessarily complicated by low capillary resistance. Rusznyak and Szent-Györgyi (18) found that "in certain pathological conditions characterized by increased permeability or fragility of the capillary wall, ascorbic acid is ineffective, while the condition can readily be cured by administration of extracts of Hungarian red pepper or lemon juice." A substance isolated from these concentrates was named "citrin" (19). An analysis of this substance showed it be be a mixture of hesperidin and eriodictin (20), and that the active principle is hesperidin.

Lindheimer *et al.* (21), after a review of the literature, concluded that "a synergism of vitamin C and vitamin P is suggested by some studies, whereas others indicate that vitamin P acts by itself." Bentsath and Szent-Györgyi (22) reported that "vitamin P requires for its activity the presence of traces of ascorbic acid. In the entire absence of ascorbic acid, vitamin P is inactive." It is the consensus that this is true conversely—"Ascorbic acid cannot function in the absence of hesperidin." This is in agreement with the concept of Warter *et al.* (23), who suggested that hesperidin is essential for the absorption and retention of vitamin C, acting synergistically to maintain normal capillary

resistance. Beiler and Martin (24) demonstrated synergism between hesperidin and ascorbic acid by the inhibitory action on hyaluronidase. Selsman and Horoschak (25), on the basis of their clinical observations, suggested that the utilization of vitamin C for the intercellular substance is dependent on the presence of hesperidin.

It is the purpose of this communication to report our observations with hesperidin and ascorbic acid in the treatment of 42 patients with rheumatoid arthritis and 17 patients with osteoarthritis, closely observed over a period of seven years.

CLINICAL MATERIAL AND PROCEDURE

Rheumatoid arthritis group

The 42 rheumatoid arthritis patients were selected because they were in the active phase of the disease. Capillary fragility and capillary permeability were manifested in spontaneously occurring petechiae or ecchymotic areas, or in strongly positive results with the capillary fragility test.

The capillary fragility test consisted of a positive cuff-pressure equivalent to half the sum of the systolic and diastolic blood pressures applied for seven minutes on the arm just above the crease of the elbow. The inner aspect of the arm was examined five minutes after removal of the pressure cuff and the number of petechiae observed. Only patients showing showers of petechiae were accepted for this study.

The sex distribution in this group was 27 females and 15 males, ranging in age from 23 years to 58 years (average, 44.6 years). The duration of the disease ranged from eight months to fourteen years, with an average of 8.7 years.

Approximately half of these patients had observed the spontaneous occurrence of ecchymotic areas on arms, legs, thighs or body. They were not subjected to the positive cuff-pressure test, which was used only in the patients not showing this spontaneous phenomenon. Capillary fragility was determined at three successive two-week intervals, and the findings were strongly positive on all three occasions.

Blood pressure tended to be somewhat low in most of these patients. Tachycardia was observed frequently and the sedimentation rate of the red blood cells was accelerated. These observations indicated the activity and severity of the arthritic process.

Osteoarthritis group

The 17 patients in this group were selected because they had unequivocal clinical evidence of osteoarthritis; they were obese, hypertensive, and manifested capillary fragility as determined by the cuff-pressure test.

There were 11 females and 6 males, ranging in ages from 47 years to 79 years (average, 59.2 years). They represented persons from various socio-economic levels, the majority being from the so-called middle class. Heberden's nodes were present in 7 of the female patients, but not in the remainder of the group.

Method of treatment

A first-phase plan was set up, applicable to both groups. A careful and complete history, including dietary habits, was obtained in every case at the start of the study. Each patient was given a thorough physical examination. Blood pressure readings were taken at least three successive times at five-minute intervals and the average recorded. Capillary fragility tests were made at four-week to six-week intervals.

Laboratory studies, including differential blood counts, urine analyses, and blood sedimentation rates, were made at frequent intervals.

In a previous report (2) we suggested that "the correction of abnormal capillary fragility in rheumatoid arthritis patients should be considered as only one phase to improve all angles of the patient's condition. This phase of treatment may enhance the efficacy of other instituted therapeutic procedures.

In the first portion of this study treatment was carried out with tablets of Hesperidin-C[1], each tablet containing 50 mg. of hesperidin and 50 mg. of ascorbic acid. Later, a capsule containing 100 mg. of each of these substances was made available (Hesper-C).[1]

In the most severe cases of the rheumatoid arthritis group, treatment was started with 600 to 1,000 mg. of hesperidin-ascorbic acid daily; when improvement in the capillary fragility was manifested, the dosage was gradually decreased to 300 mg. daily, which represented our maintenance dose. In the milder cases, we gave 400 to 600 mg. and gradually decreased the dosage to a maintenance level of 300 mg. The Hesperidin-C or Hesper-C was prescribed in divided doses after meals and at bedtime.

In the osteoarthritis group, treatment was started and maintained with 300 mg. of Hesperidin-C or Hesper C in divided doses taken after meals.

The reason for the variation in dosage between the rheumatoid and osteoarthritic groups is obvious. In the former there is an active inflammatory process which taxes the capillary resistance to a greater degree than in the latter.

OBSERVATIONS OVER A SEVEN-YEAR PERIOD

Rheumatoid arthritis group

1. Normal capillary resistance was established in six to eight weeks from the beginning of hesperidin-ascorbic acid therapy and was maintained in 35 of the 42 patients.

2. In 5 patients, the readings were on the border line; at no time were normal results obtained.

3. Two patients who did not at any time manifest normal capillary resistance were lost to the study in the third and fifth years; 1 died of pneumonia and 1 died following a major surgical operation.

4. Fusiform swellings were reduced more quickly in those patients in whom normal capillary resistance was established, compared to those in whom capillary fragility persisted.

[1] Hesperidin-C and Hesper-C: The National Drug Company, Philadelphia, Pa.

5. Protein hydrolysate[2] and B complex were apparently more readily utilized in the patients treated with Hesper-C, as manifested by a gain in weight and an increase in the hemoglobin level and red blood cell count.

6. The sedimentation rate was favorably influenced, concomitantly with the reduction in the fusiform swellings.

7. With the improvement in the arthritis, the blood pressure in most of the patients ranged within normal limits.

8. Some of the patients, who had reported susceptibility to upper respiratory infections, were apparently benefited by the use of Hesper-C and ascribed their continued improvement to the acquired resistance to colds. (This is offered as their own observation, and does not necessarily reflect our impressions or conclusions.)

9. The withdrawal of Hesper-C for several months in a few of the patients resulted in flare-ups of the arthritic process, which required larger doses and a longer period of administration for control.

10. No patient was lost as a result of vascular accidents.

Osteoarthritis group

Among the 6 male patients in this group, the osteoarthritis was associated with arteriosclerosis in 3, and was traumatic in the other 3. Among the 11 female patients, it was associated with the menopause in 3, with obesity in 5, and with arteriosclerosis in 3.

Therapy was essentially directed toward the designated etiologic factors. Because of easy bruisability in the menopausal women, and because of the vascular involvement in the peripheral vascular types, hesperidin-ascorbic acid was considered a necessary adjuvant in treatment. Dietary restrictions in the obese patients were considered an adequate reason for the use of this therapy. Results, over a 7-year period, were as follows:

1. One of the arteriosclerotic male patients suffered from a cerebrovascular accident in the second year of the study. He recovered within three months, and continued to do well under a program of limited activity.

2. In the menopausal women, resistance to easy bruisability was manifest within an average of six weeks after starting hesperidin-ascorbic acid, and there were fewer complaints.

3. In the obesity group, 1 patient died from cardiac failure in the third year of our observation period. The remaining 4 adhered to their diets diligently and their improvement continued throughout the study. In 2 of these patients, capillary resistance was within normal limits, and in 2 it was improved.

4. In the 6 patients with hypertension (arteriosclerosis), blood pressure was reduced to the normal range. Although this could have been the result of rest and diet, in addition to the Hesper-C, it is difficult to deny the drug some credit.

5. The arthritic processes appeared to be benefited. Despite the irreversible articular lesions, these patients experienced less fatigue, less discomfort in the joints, and general improvement.

[2] Protinal or Vi-Protinal: The National Drug Company, Philadelphia, Pa.

SUMMARY

Long-term observations are presented on 42 patients with rheumatoid arthritis and 17 patients with osteoarthritis, in whom hesperidin combined with ascorbic acid was used as a therapeutic adjuvant in the form of Hesper-C. It is demonstrated that this combination has the capacity to correct abnormal capillary fragility and permeability, and thus enhances the efficacy of therapy directed against the disease state.

In the treatment of arthritis, attention should be focused on the patient as a whole, rather than on the joints and bones. The capillary system plays a major role in the economy of the body, and thus deserves attention at all times. The therapeutic management of arthritis is more effective in the presence of normal capillary resistance.

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NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED. XIII. GENERAL MANAGEMENT OF NORMAL INDIVIDUALS AFTER THE AGE OF 80*†

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No one has yet been able to define problems of aging in a fashion acceptable to everyone. It may be presumed that aging represents the changes that take place in the organism with the passage of time, with particular emphasis on the period following the cessation of growth. Aging begins when growth stops. Growth and aging are incompatible (1).

The term "arteriosclerosis" refers to several distinct pathologic entities which cause thickening of the blood-vessel wall. It embraces such conditions as atherosclerosis, Mönckeberg's sclerosis, arteriolosclerosis, and hyperplastic arteriosclerosis. Recent investigations have been most numerous in the field of the etiology and pathogenesis of atherosclerosis, since among arteriosclerotics this is the lesion which is the chief cause of morbidity and mortality (2).

Numerous attempts have been made to develop a biochemical procedure for prognosis and diagnosis in this insidious condition. An elevated level of serum cholesterol (3–5), abnormalities of lipid fractions (6), an abnormal ratio of cholesterol to phospholipid (7, 8), and a qualitative disturbance of serum lipoprotein fractions have all in turn been pointed to as the important factor (9, 10). It is, however, becoming increasingly obvious that no one single factor is significant.

For the past five years we have been engaged in an intensive study of lipid metabolism. Five hundred individuals ranging in age from 13 to 100 years (average, 46 years) were observed, in an attempt to determine which laboratory and clinical criteria are definitive in diagnosing atherosclerosis, and which methods are useful in its management (11–14). With the exception of the increased total serum cholesterol, phospholipid and total lipid values in patients with acute coronary and myocardial infarction (15–17), we have found that serum lipid values may vary to such an extent as not to be of clinical aid. All of the serum lipid fractions must be determined in order to reflect the true state and disturbance of the blood lipid. For the past three years biochemical studies have been made in 100 normal subjects who ranged in age from 80 to 100 years (average, 86 years) (18–20). These elderly folks, who were institutionalized for custodial care rather than for medical reasons, had no previous history of coronary attacks, cardiac, endocrine, metabolic or venereal diseases, and were considered to be "normal."

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† Aided by a grant from the Sophie D. Cohen and William W. Cohen Foundation.

METHODS OF STUDY

Blood chemical determinations were performed for creatinine, nonprotein nitrogen, and serum lipid partitions such as total cholesterol, phospholipid, neutral fats and serum lipids (11). Serum lipoprotein molecules (Sf 0–12 and Sf 12–400) were differentiated by means of the high-speed ultracentrifuge apparatus. The significance of the atherogenic potentialities derived from the Sf lipoprotein molecule values, was indicated by the atherogenic index (21). Alpha and beta globulin fractions were obtained by paper electrophoresis, for comparison and correlation with the Sf molecule values (22). Ophthalmoscopic and autopsy studies were also correlated. Electrocardiograms and roentgenograms were obtained. We approached our studies with an open mind, since no previous data in such an age group had appeared in the literature.

CASE REPORTS

The problems that may confront the physician today in treating geriatric patients are illustrated by the following case reports:

Patient T.D.

This 100-year-old man, of Irish descent, had been in the city home for a period of twenty-five years before he was transferred to the Bird S. Coler Hospital in September 1952. While at the city home he had had a cataract extraction, a fracture of the left hip, dermatitis and dermatophytosis.

Diagnosis on admission to the hospital was generalized arteriosclerosis, arteriosclerotic heart disease, cataract, dermatitis and senility.

The family and medical histories were of no significance. His habits involved tobacco and coffee but no alcohol. His social history was that of a motorman on a railroad, with little earning capacity. He had no interest and no hobbies.

Physical examination on admission showed the following: The patient was alert and cooperative at times. There was no vision of the left eye due to a previous cataract operation. He had a full set of dentures. The chest was emphysematous in type. There was a loud cardiac systolic murmur with a regular rhythm. The blood pressure was 100 systolic and 50 diastolic. There was a right inguinal hernia. The skin was dry and scaly.

Laboratory data. There was no anemia, but slight azotemia. The peripheral blood findings were: Hgb. 13 Gm.; RBC 4,100,000; WBC 7,000; polymorphonuclear cells 61 per cent; lymphocytes 39 per cent. Chemical analysis of the blood showed the following levels: urea 26 mg.; creatinine 4.2 mg.; and sugar 91.2 mg. per 100 ml. The urine was normal. *Serum lipid* studies showed low values (mg. per 100 ml.) as follows: total lipids 559 mg., phospholipids 170 mg., and total cholesterol 147 mg.; the P/C ratio was 1.16. *Lipoprotein* molecular values were: Sf 0–12 = 206; Sf 12–20 = 24; Sf 20–100 = 28; and Sf 12–400 = 67. The atherogenic index was 32 units (Table 1).

X-ray examination of the chest showed an enlarged heart with an elongated aorta. There was bronchiectasis of both lower lung fields and dextro-scoliosis of the dorsal spine.

Course during hospitalization. A short time after admission, it was noted that the patient was drowsy and had difficulty in keeping awake. Examination showed no evidence of an accident or of a cerebral condition. The drowsiness was considered to be a reaction to barbiturates (phenobarbital), which the patient had been taking for a considerable period of time before admission to the hospital. The condition cleared up on discontinuation of the medication.

The patient was permitted out of bed to prevent any complications and weakness, in spite of the healed old fracture of the left hip. He received due attention and care and was

TABLE 1

Arithmetic Mean Values of Serum Lipid Partition, Lipoprotein Molecules, and Atherogenic Index in Normal Subjects (Middle Aged and 80–100 Years of Age)

	Normal Subjects			
	Male	Female	Male	Female
	(49 yrs.)	(44 yrs.)	(80–100 yrs.)	
Serum lipid partitions				
Phospholipids (mg./100 ml.)	220	216	194	192
Total cholesterol (mg./100 ml.)	200	192	203	230
Cholesterol esters (mg./100 ml.)	125	119	126	161
Free cholesterol (mg./100 ml.)	75	76	77	69
Neutral fats (mg./100 ml.)	342	380	196	264
Total lipids (mg./100 ml.)	846	870	611	645
Ratio of phospholipids to total cholesterol (P/C ratio)	1.26	1.10	0.95	0.83
Lipoprotein molecules (mg./100 ml.)				
Sf 0–12	361	324	293	305
Sf 12–20	76	70	36	43
Sf 20–100	109	78	43	46
Sf 12–400	206	158	131	128
Atherogenic index (unit values)	74.0	61.0	53.0	53.2

(From *A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

kept in a wheel chair with proper precautions. However, at a time when no attendant or nurse was in the patient's vicinity while meals were being served, he untied himself from the wheel chair, slipped to the floor and experienced an intertrochanteric fracture of the right femur with marked coxa vera. This necessitated confinement to bed, because of Russell traction and intravenous therapy.

A week later, pneumonia developed, with a slight rise of temperature. The patient became confused, uncooperative, and weak. There was a breakdown of the skin in the left sacral area. Three weeks after acquiring the right hip fracture, the patient died.

Patient C.B.

This man of Greek extraction, aged 87, had been in the city home for five years before admission to the Bird S. Coler Hospital in 1952. His hospitalization lasted eighteen months.

The diagnosis on admission was arteriosclerotic heart disease, osteoarthritis, bronchiectasis of the right lung and aplakia.

Physical examination on admission showed the patient to be well developed. There were rales at both lung bases. The heart sounds were normal. The blood pressure was 120 systolic and 80 diastolic.

Laboratory examination revealed a mild anemia with Hgb. 14 Gm.; RBC 3,565,000; WBC 10,800; polymorphonuclear cells 74 per cent; immature forms 5 per cent; and lymphocytes 21 per cent. The level of blood urea was 16 mg., creatinine 2.5 mg., and sugar 70 mg. per 100 ml. The urine was normal. *Serum lipid* studies showed low values (mg. per 100 ml.) as follows: total lipids 604 mg., total cholesterol 212 mg., and phospholipids 208 mg.; the P/C ratio was 0.98. *The lipoprotein* molecular values were: Sf 0–12 = 262; Sf 12–20 = 33; Sf 20–100 = 26; Sf 12–400 = 87. The atherogenic index was 42 units (Table 1). The *electrocardiogram* was normal.

X-ray examination showed a cardiac enlargement with a calcified aortic knob, calcified femoral arteries, and advanced hypertrophic spondylosis. There was a dipahragmatic hernia of the colon, with upward displacement of the stomach.

Course during hospitalization. The patient had an attack of pneumonia and abdominal pains with vomiting, from which he recovered. A year later, signs recurred in the left lung, which were considered to be indicative of pneumonia with atelectasis. The diaphragmatic hernia was thought to be causing pressure in the mediastinum. The patient died within a month.

Postmortem examination showed bronchogenic carcinoma of the left lung with pleural fluid, a thickened aortic valve leaflet, and fatty metamorphosis of the liver.

The foregoing cases represent the problems that may arise in treating people in the geriatric age group. Barbiturates are not to be given over an extended period of time, since some reaction may occur, as in Patient T.D. Constant vigilance is essential; otherwise some innocent action on the part of the patient may have serious results—such as a hip fracture. The age period of 80–100

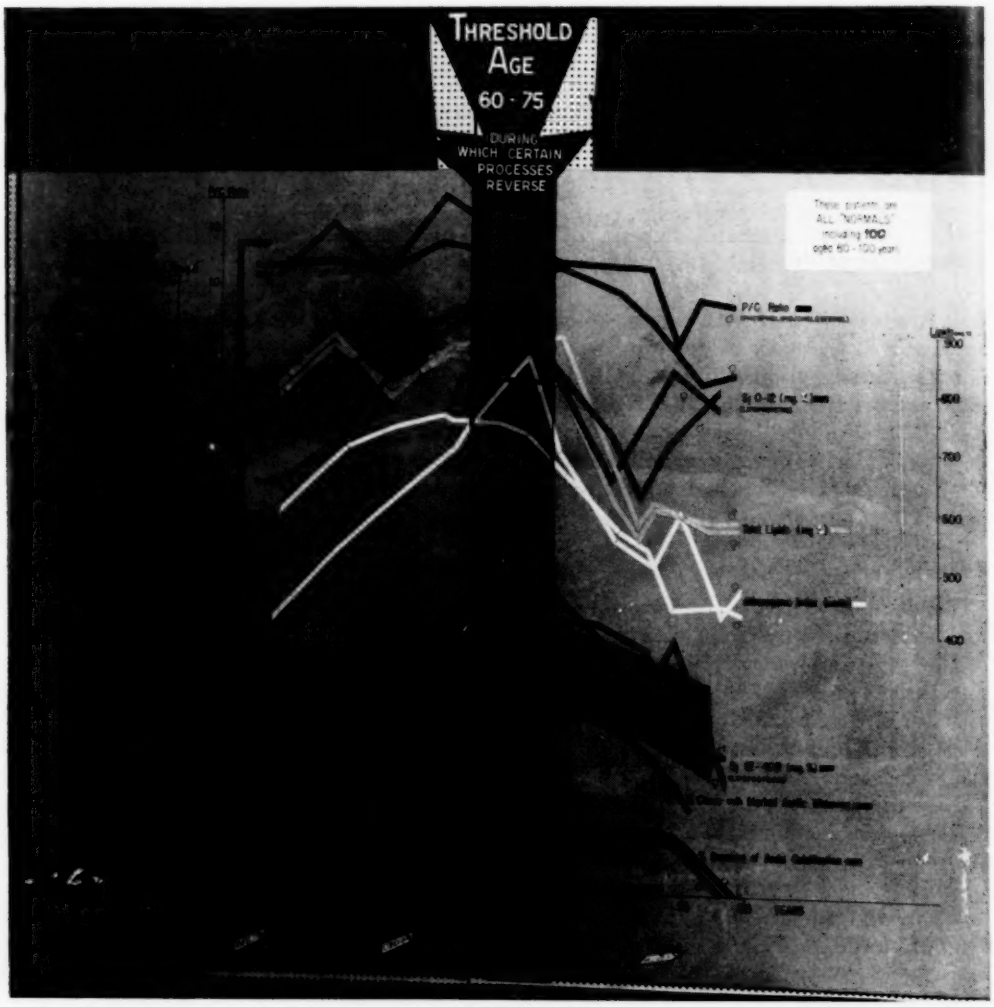

FIG. 1. "Threshold age" (60–75 years) after which there is a reversal of biochemical and/or physical processes. (*A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

years is one of accidents rather than incidents; therefore caution is needed in order to prevent fractures.

In the second patient the attacks of vomiting and abdominal pains were considered due to the diaphragmatic hernia, a condition which is frequently symptomless in this age group. However, the clinically diagnosed pneumonia proved to be due to bronchogenic carcinoma. Although the incidence of malignancy in this age group is not high, it behooves the physician to consider such a diagnosis in many unexplained conditions.

THRESHOLD AGE

We observed that a threshold occurs in the 60 to 75 year group ("threshold age"), after which there is a reversal of biochemical and/or physical processes (Fig. 1). Correlations were found between x-ray and biochemical data in the presence of microscopic atherosclerosis, which were not in agreement with previously accepted criteria. The values reached the levels found in middle age. These normal individuals aged 80 to 100 years may acquire their "second youth" again and this may explain why they attain such an age. The life span may be divided into a race of four "hurdles" or groups: 1) *youth*—infectious diseases; 2) *middle age*—coronary and heart diseases; 3) *late middle age*—malignant diseases). In the threshold period (60–75 years) biochemical processes become reversed.) 4) *old age*—frequent accidents (23).

NEWER LABORATORY CONCEPTS

The results of serum lipid partition related to total cholesterol and phospholipids are inconclusive. A ratio of phospholipids to cholesterol (P/C ratio)

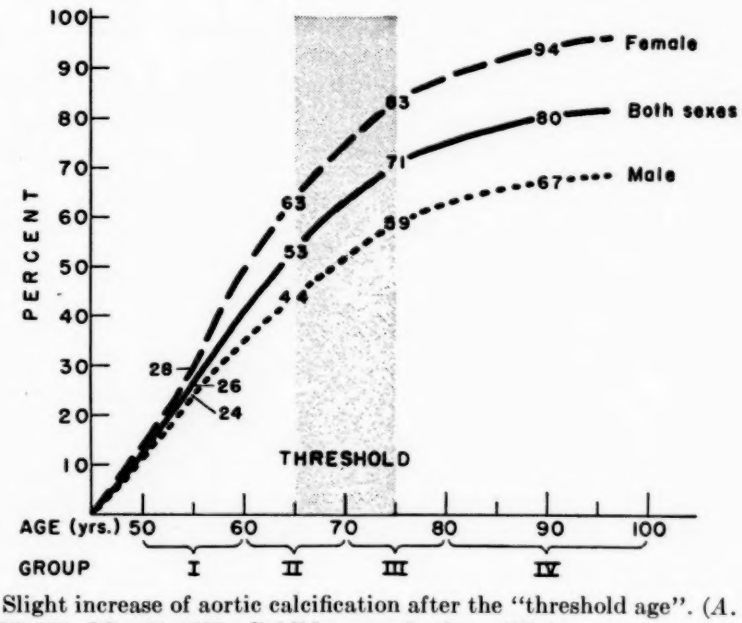

FIG. 2. Slight increase of aortic calcification after the "threshold age". (*A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

less than 1.00 does not imply atherosclerosis (14). The lipoproteins (ultracentrifuge) and the atherogenic index become reversed in the "threshold age" (Fig. 1).

Electrophoretic (paper method) determinations show no direct correlation with ultracentrifuge determinations of lipoproteins (22).

There are no electrocardiograms which are typical of the aged, since 71 per cent presented a normal pattern. Ballistocardiograms are unsatisfactory because of technical difficulties caused by rigidity and tremors. Elevated blood pressure readings in the aged usually are not to be regarded as "normal" for the age. Ophthalmoscopy is a supportive method for the diagnosis of arteriosclerosis.

NEWER ROENTGENOLOGIC AND PATHOLOGIC CONCEPTS AND INTERPRETATIONS

Calcification of the aorta progresses more rapidly in females. The rise until the "threshold age" is sharp; then, the increase is comparatively slight (Fig. 2).

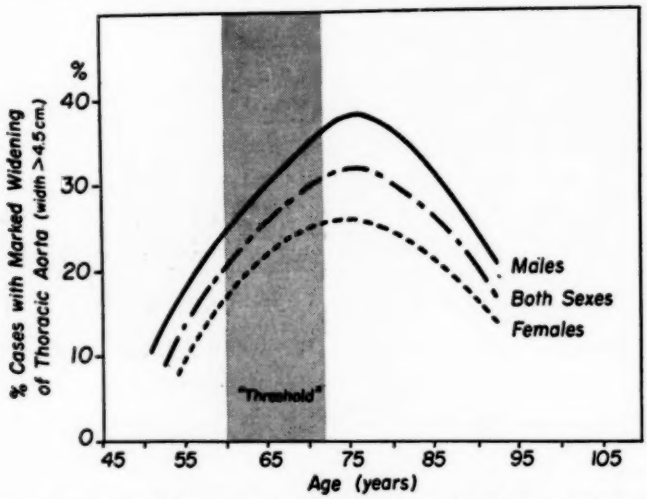

FIG. 3. Decrease in the incidence of aortic dilatation in the ages after "threshold age". (*A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

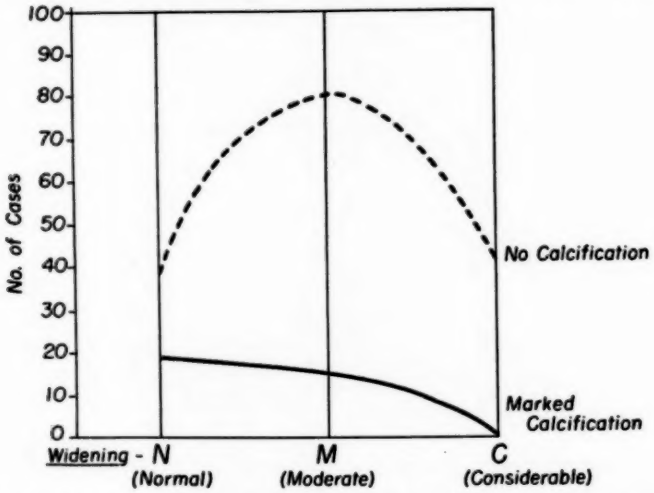

FIG. 4. Marked widening of aortic arch is not associated with marked calcification. (*A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

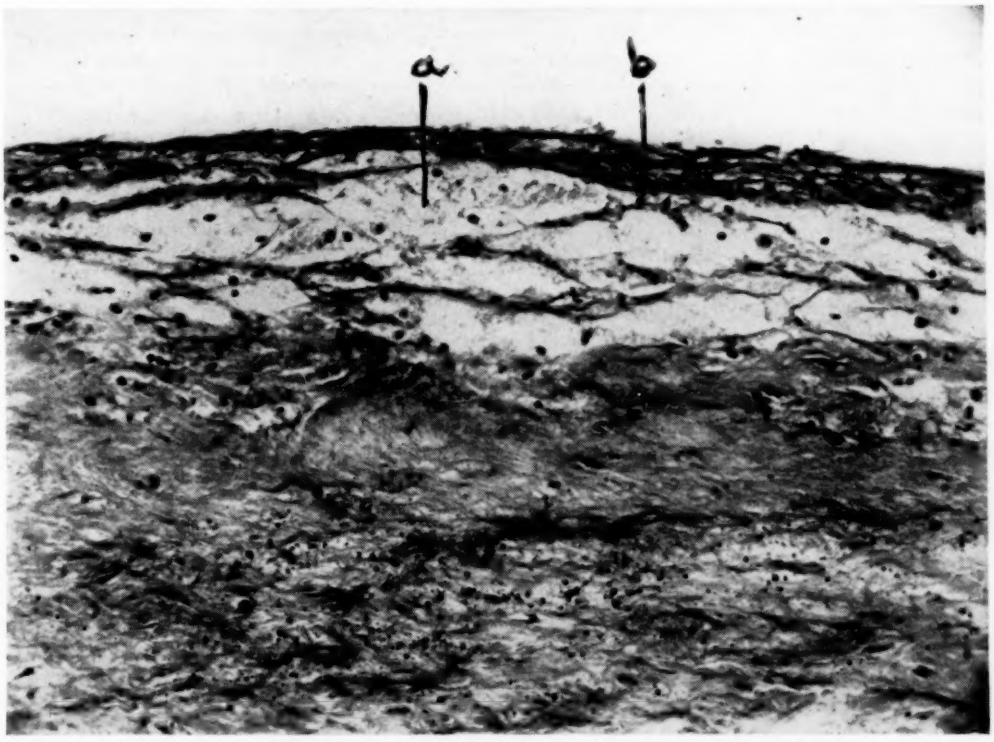

FIG. 5. High-power magnification of a fibrosed aortic intima. Lipid laden macrophages (a–b)—representing recent lipid imbibition. (*A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956—Goldbloom and others (23).)

Aortic dilatation is more frequent in males. As it reaches the "threshold age"—around 70 to 80 years—the incidence decreases with age in both sexes (Fig. 3). Marked aortic widening is usually not associated with marked calcification in either sex (Fig. 4). Calcification of the aorta is not correlated with abnormal biochemical findings, whereas dilatation is.

Pathologic (autopsy) findings are somewhat equivocal. There is no appreciable correlation with the chemical laboratory findings, but there is with the x-ray findings. In some of the aortas examined, evidence of lipid imbibition was found in the innermost coats (Fig. 5). This is similar to the early changes found in the aortas of rabbits which are fed large amounts of cholesterol and is considered by some to simulate "active atherosclerosis."

THE ROLE OF THE GERIATRICIAN

Our studies support an attitude of hope and non-defeatism in treating geriatric patients (Table 2). There are many procedures the physician should carry out, and many that he should avoid. Hypertension may be controlled; retinal hemorrhage may be diminished; tremors and spasticity may be helped; and pain from osteoporosis (thinning of the bones) may be relieved by hormones. Since there is such proneness to accidents in this age group, these patients must be instructed to minimize the danger. Rehabilitation is an important factor in alleviating and comforting these oldsters.

TABLE 2

What the Geriatrician:.....	Should Prescribe	Should not Prescribe
DIET.....	Liberal balanced diet. Correction of obesity.	Low caloric–low fat diet.
LIPOTROPIC AGENTS....	Only if liver is damaged or fatty.	Not specific for human atherosclerosis.
HYPERTENSION.....	Control by anti-hypertensive agents.	The disregard of elevated blood pressure.
PERIPHERAL VASCULAR CONDITIONS.....	Deliberate examination. Vasodilators, proper hygiene and physical measures. Feet lowered; skin soft; shoes wide.	Extremes of temperature locally. No tight or elastic bandages.
OPHTHALMOLOGY.....	Examination for cataracts, glaucoma, vitreous opacities and retinal changes	Atropine for dilatation and examination of eyes.
RETINAL HEMORRHAGE.	Water-soluble bio-flavonoid compounds.	Local eye applications of extreme heat and cold, or promiscuous use of antibiotics locally.
AGITATION.....	Chlorpromazine and chloral usually safe and effective.	Barbiturates, as in the aged they may cause further excitation and other harmful effects.
TREMOR; SPASTICITY...	Proper selection and combination of drugs for akinesia, rigidity and tremor.	Immobilization; splinting. Should not allow distorted body posture.
HORMONES—OSSEOUS PAIN.....	Androgens and estrogens (simultaneously), as they often relieve osseous pain	Analgesics alone, as they merely mask osseous pain and are of no direct value.
ANTICOAGULANTS.....	Heparin—safer than oral anticoagulants.	Oral anticoagulants dangerous in liver, renal, and ulcerating pathologic conditions.
ACCIDENTS.....	Instructions, to minimize accidents such as hip fracture—the common accident in the aged.	Vegetation as a means of avoiding accidents.
REHABILITATION.....	Graded physical exercise and mental occupation. Well planned environment.	A defeatist "do nothing" attitude.

(From *A. M. A. Arch. Int. Med.* **97:** 359 (March) 1956 —Goldbloom and others (23).)

As a result of our studies, the physician is warned *not* to prescribe or perform procedures that may be harmful, such as low caloric-low fat diets; lipotropic agents, unless the liver be damaged or fatty; atropine, and promiscuous use of local antibiotic preparations for eye conditions; or excessive amounts of barbiturate preparations. An elevated blood pressure should not be ignored. These patients should not be immobilized, put in splints, or allowed to assume a distorted body posture. Oral anticoagulants are dangerous in liver, renal and

ulcerating (ulcer) conditions. The aged should not be allowed to vegetate and assume a "do nothing" attitude.

SUMMARY AND CONCLUSIONS

1. The lipid metabolism has been studied in 100 normal individuals 80–100 years of age.

2. The serum lipid partition fractions, lipoprotein molecules, and the atherogenic index increase from youth until the age of 60 to 75 years—the "threshold age."

3. There is a decline or reversal of biochemical and/or physical processes in the "threshold age."

4. Marked aortic widening is usually not associated with marked calcification in either sex.

5. Current treatment of atherosclerosis in normal geriatric individuals is discussed, especially with regard to what the geriatrician should do and not do in the line of therapy.

6. The physician is warned not to adopt a defeatist attitude and do nothing.

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NUTRITION IN PREVENTIVE GERIATRICS

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The prevention of deterioration and disability as well as the treatment of disease is increasingly important in geriatrics (1). The incidence of degenerative disorders, which account for the major portion of disease and infirmity in the aged, is increasing in the United States and seems to defy control. Recently, White and Jolliffe (2) reported to Congress that it is more hazardous to be a man between 40 and 65 years of age in the United States than in any other country with reliable statistics. They suggest that the high standards of living in this country are probably the cause of the marked increase in heart disease.

What is the reason for this critical state of health? Recent biochemical research has shown that imbalanced nutrition is a major cause of degenerative changes in the body. Prevention, through the employment of sound nutritional principles, appears to be the most efficient and economical method of controlling degenerative diseases.

QUALITY OF FOODS

Abandoning a static attitude towards nutrition, and re-examining nutritional problems, we find that little or no attention is paid to the quality of foods. A given food is commonly assumed to have a constant nutritional value. However, vegetables may vary up to 200 per cent in mineral content and as much as 100 per cent in protein content (2, 3, 4). The protein content of such staple foods as wheat and corn has gradually decreased; ten years ago the protein content of corn was 9.5 per cent, but today the average is 8.5 per cent.

The protein and carbohydrate content of foods is largely determined by the fertility of the soil. Two-thirds of the top soil in the United States has been shown by soil analysis to be deficient in minerals and in organic matter. Only the mid-continental section of the country has the soil fertility and mineral ingredients necessary for the production of high quality protein. Variants in the structural composition of the protein molecule may make the difference between health and disease. Albrecht at the University of Missouri found the proteins in plants grown on fertile soil to contain a high percentage of two of the essential amino acids, lysine and tryptophane. He showed by animal feeding tests that these high quality protein plants produced animals with less fat, greater stamina, higher resistance to disease, and a better reproductive record.

Twenty-four or more minerals are believed to be necessary for the maintenance of human health; the number may be as high as 70. Trace minerals are activators of the enzyme system, and there is an active exchange of trace minerals in bone. Silicon is related to calcium and produces elasticity in bones and skin. This chemical reaction diminishes with age. Barnett (5) compared healing rates for

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the same type of fracture in two counties in Texas. Consistent chemical findings indicated that an optimal fluorine, a high iodine, and a high magnesium intake and all the known essential trace elements, were necessary for proper bone healing. The rate of healing was one-third greater in Deaf Smith County—the soil, water, and plants of which contained these elements. This suggests that a deficiency of trace minerals in the soil may have some bearing on osteoporosis and other bone diseases frequently found in older people.

The chemical differences in food defy appraisal by the consumer. New standards are necessary so that quality foods can be properly labeled.

UTILIZATION OF FOODS

Food is of no value unless it can be utilized by the body. The vitamins and minerals necessary for assimilation and utilization may be depleted by the refinement of foods. These elements, for example, have been only partially replaced by the "enrichment" of breakfast foods and bread. With highly refined foods, the body cannot maintain its structural integrity or release sufficient energy to maintain optimum strength. Toxic metabolites form as a result of incomplete metabolism, especially of carbohydrates. When sufficient amounts of vitamin B complex are lacking, the approximately 500 calories per day of refined sugars consumed by the average person cannot be reduced to the normal end-products, carbon dioxide, water and energy. Incomplete carbohydrate metabolism results in the formation of excessive amounts of pyruvic and lactic acids. Chemists have shown that this incomplete metabolism causes the death of tissue cells, which later may cause a pathologic condition in vital organs.

Another result of an increase in carbohydrate intake is, of course, obesity. The nutritional studies of McCay, Maynard, Sperling and Osgood (6) show that the retention of youthfulness and "longer life with a smaller percentage of years of dependency" can be had by restricting calories and increasing consumption of protective foods. The selection of foods should be based on their effects on body cells rather than on their satisfaction of the appetite.

CONTAMINATION

Food of poor nutritional quality is only one of the health problems today. All foods contain a residue of insecticidal sprays. The United States Public Health Service (7) reported in 1954 that analysis of 25 meals selected at random from restaurants and institutions revealed DDT in all of them. It was found even in meat, fried and mashed potatoes, pie, and coffee with cream. The conclusion was that "few if any foods can be relied upon to be entirely free of DDT."

On analysis of human fat tissue (8), evidence of DDT accumulation was found in 23 of 25 specimens, and 28 per cent contained 5 parts per million or more. Five parts per million will cause liver damage in rats. Human fat should contain no DDT because DDT has a direct toxic effect upon the central nervous system as well as upon other vital organs (8).

Chlorinated hydrocarbons interfere with the activity of enzymes in the body

and thus indirectly influence all metabolic reactions. The effects of Parathion, a phosphate insecticide, on the enzymes of muscle metabolism are well established. Determination of the blood level of cholinesterase is now used to detect Parathion poisoning in persons who use this insecticide as a spray (9).

Other chemicals are present in and on foods, for which further long-range studies are necessary to determine their effect upon health. The Food and Drug Administration recently found three coal tar dyes used for coloring foods to be harmful and restricted their use: Orange No. 1, used to color candies, soft drinks, and sausages, as well as many other foods; Orange No. 2, used for the same purpose; and Red No. 32, used to color oranges. The Cancer Prevention Committee found these dyes to be carcinogenic in animal tests and so reported at a Senate Hearing. Many similar dyes are still in use and being consumed by the public.

Most capons on the market contain a residue of stilbestrol, following its use as a pellet in the neck in sufficient strength to cause chemical castration. Stilbestrol has recently been added to cattle food to increase body weight rapidly before sending the cattle to market. The only value of this practice is economic; there is no evidence that it improves the nutritional value of food. Stilbestrol accumulates in the liver; therefore, beef liver may be a health hazard, because of the castrating effect of stilbestrol in the male. Beef is something we eat for a lifetime. Canada, after careful investigation, has outlawed the use of stilbestrol in food production.

The fluoridation of city water is another controversial subject related to nutrition. As Barnett (5) showed in his bone studies, it was not fluorine alone that produced healthy bones and teeth in Deaf Smith County. All trace elements had to be present in balanced proportion. Many reports have indicated that fluorine is potentially dangerous to elderly people. According to Spiro (10), fluorine interferes with calcium metabolism and may cause osteoporosis. Mass populations should not be subjected to fluoridated drinking water while there is reason to anticipate harmful effects.

SUMMARY

Degenerative disease can probably be controlled efficiently and economically through preventive measures based on sound principles of nutrition. Adequate nutrition may be difficult to achieve because: 1) Two-thirds of the top soil in this county is deficient in minerals and organic matter and therefore produces food of low quality. 2) The refinement and processing of foods removes essential vitamins and minerals. 3) Foods may contain residues of potentially toxic insecticides. 4) Dyes that may be carcinogenic are used extensively to improve the appearance of certain foods. 5) Sufficient long-range study has not been made of the effects on the human body of antibiotics and stilbestrol fed to animals raised for food. 6) The fluoridation of city water is a controversial subject; the ultimate effects may be harmful. All of these long-range problems influence the development of degenerative diseases.

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RHEUMATOID ARTHRITIS COMPLICATED BY SEVERE ULCERATIVE COLITIS, SUCCESSFULLY TREATED WITH PREDNISONE AND RAUWOLFIA. A CASE HISTORY

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The etiology of chronic ulcerative colitis is not known. Prednisone, although not curative, has given highly favorable results in some cases. The following case history is of particular interest because of the coexistence and possible interrelation of rheumatoid arthritis and chronic ulcerative colitis.

CASE REPORT

A 55-year-old woman, who had first been seen in July 1949 at the age of 49 years, at which time she had just recovered from pneumonia, now complained of abdominal pain and frequent bowel movements with blood and mucus in the stools.

She had a history of rheumatoid arthritis dating from 1939.

A review of her early history disclosed diphtheria and jaundice at the age of 4 years. Of her 3 children, 1 was an invalid from progressive muscular dystrophy. Cholecystectomy and appendectomy had been performed in 1928. A simple diarrhea in 1943 lasted for three weeks but responded to customary treatment. Diarrhea associated with blood and mucus in the stools, tenesmus, abdominal pain, fever and loss of weight developed five months later. Recurrences, lasting from a week to a month, with 15 to 20 bowel movements a day and associated extreme fatigue, malaise, anorexia and loss of weight, necessitated hospital admission in 1944. A barium enema and sigmoidoscopic examination showed chronic ulcerative colitis. The patient was given aluminum hydroxide gel (Amphojel) and a salt-free bland diet. Treatment with sulfonamides and penicillin had little effect on the colitis.

Physical examination in July 1949 revealed that the arthritis involved almost all of the large and small joints of the extremities. Examination of the mouth showed pyorrhea. The heart and lungs were normal. The liver was palpable, and the sigmoid and ascending colon were tender and cord-like. The reflexes were normal, and the blood pressure was 140/84. The erythrocyte sedimentation rate was 46 mm. per hour, leukocytes 8,650 and erythrocytes 4.58 million per cu. mm. Results of stool culture for *Shigella Salmonella* and examination of stools for amoebae and parasites were negative. The bacteria count (Henderson-Seneca) was 670 billion total, with 650 million coliform organisms per gram of wet feces. The patient was given a low-fat, high-protein and high-vitamin diet. Phthalyl-sulfacetamide (Thalamyd) was administered in a dosage of 1 Gm. three times daily after meals for ten days. After a rest of ten days, 250 mg. of chlortetracycline was given four times daily after meals for five days. Phthalysulfacetamide controlled the diarrhea, but neither chlortetracycline nor methylcellulose induced any further improvement. Phenobarbital and tincture of belladonna were also used.

In December 1949, the sedimentation rate was 36, hemoglobin 81 per cent, leukocytes 7,200, and erythrocytes 4.4 million. The bacteria count of the stools was 130 billion total, with 66 million coliform organisms. The attacks of bloody diarrhea were controlled to some extent by intermittent use of phthalylsulfacetamide. Progynon (estradiol) buccal tablets were prescribed for menopausal symptoms.

In February 1950, a daily retention enema containing 100,000 units of penicillin and 100 mg. of chlortetracycline resulted in improvement of the colitis. In June of that year, 250

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mg. of oxytetracycline four times daily after meals for five days, and iron and vitamin B_{12} injections for anemia, were begun. The sedimentation rate was 36, hemoglobin 78 per cent, and erythrocytes 4.6 million. The bacteria count of stools was 4.2 billion total, with 4 million coliform organisms. The patient responded well to alternating use of oxytetracycline and phthalylsulfacetamide but had residual symptoms.

The patient was seen twice during 1951. Her condition was good; she had two bowel movements in the morning and blood appeared in the stools only occasionally. Hemorrhoids had developed. Following hemorrhoidectomy, her health improved.

In July 1952, the bowel movements were normal but the patient's blood pressure had increased to 154/98. She was given Rutaminal and instructed not to eat salt. Rectal strictures developed and had to be dilated. In November, she reported having only two to three bowel movements a day, but the arthritis had flared up and erythema nodosum had developed. The sedimentation rate was 50 and leukocytes 6,850. Cortisone administration was begun, and the dosage increased as the arthritis gradually became more severe. Neither the colitis nor the arthritis responded to cortisone, and she lost weight and strength.

The patient's blood pressure was 142/88 in July 1953. Hydrocortisone and carbomycin were started in dosages of 10 and 500 mg., respectively, three times daily. Hydrocortisone was also injected into the joints. During administration of carbomycin the colitis improved somewhat, but the arthritis progressed. The colitis and arthritis seemed to be closely correlated, one activating the other.

A severe attack of arthritis and colitis occurred in March 1954. The blood pressure was 170–148/102–100, sedimentation rate 36, hemoglobin 72 per cent, and leukocytes 5,750. The patient was advised to move to a dry climate and avoid housework, because she was practically crippled. Oxytetracycline, vitamin B_{12} injections, vitamins, and iron were again prescribed.

Pleurisy developed in August 1954. Neither hydrocortisone, by intra-articular injection and orally, nor phenylbutazone (Butazolidin) had had any effect on the arthritis or colitis. The patient was maintained on phthalylsulfacetamide, oxytetracycline, and carbomycin. Anal pruritus caused by the latter two drugs responded to hydrocortisone ointment.

By February 1955, the patient was having dizzy spells and the ulcerative colitis and arthritis had become extremely severe. Her condition was deteriorating rapidly. Therapy with prednisone (Meticorten) was initiated with the thought that, if it were unsuccessful, colostomy or colectomy would be necessary. The patient, however, refused surgical intervention. The blood pressure at this time was 184–172/104–100. She was now given 30 mg. of prednisone daily, 300 mg. of rauwolfia (Rauxidin) daily, vitamin B_{12} injections, and carbomycin. This energetic treatment yielded dramatic results.

Although our first impression was that the prednisone was primarily responsible for the improvement in this patient, upon reflection we concluded that the concomitant administration of rauwolfia (Raudixin) may well have played a part. The tranquilizing effects of this drug and the well-known fact that patients with ulcerative colitis tend to show signs of anxiety and nervous tension convinced us that the combination of prednisone plus a tranquilizing drug (in this case, Raudixin) might prove to be a useful one in the management of ulcerative colitis.

The bowel movements became practically normal, and blood and mucus disappeared from the stools. The abdominal pain, tenderness, and tenesmus subsided. Arthritic symptoms subsided in all of the joints, except for limitation of movement in the right knee. The blood pressure fell to 144/88. Following this improvement, the dosages were gradually decreased until maintenance levels of 10 to 15 mg. of prednisone and 200 mg. of rauwolfia a day were reached on May 21. In addition the patient occasionally took carbomycin or phthalylsulfacetamide. She is free of complaints of ulcerative colitis, and the arthritis is satisfactorily controlled.

SUMMARY

Rheumatoid arthritis of sixteen years' duration and chronic ulcerative colitis of more than eleven years' duration in a 55-year-old woman each had progressed

despite therapy. Of the various drugs given to relieve the colitis, phthalylsulfacetamide controlled diarrhea, and penicillin, chlortetracycline, oxytetracycline and carbomycin effected some temporary improvement. The arthritis remained unrelieved, although hydrocortisone, cortisone and phenylbutazone were given; meanwhile hypertension developed. Finally, the arthritis and particularly the colitis became so severe that colostomy or colectomy seemed mandatory. Prednisone given in combination with rauwolfia promptly relieved the symptoms. Under therapy, the elevated blood pressure was significantly reduced and the diarrhea and ulcerative colitis were satisfactorily controlled. This case indicates a definite relationship between chronic ulcerative colitis and rheumatoid arthritis. The former may be related to the collagen group of diseases.

Abstracts of Current Literature

INFLUENCE OF SEX AND SEX HORMONES UPON THE DEVELOPMENT OF ATHEROSCLEROSIS AND UPON THE LIPOPROTEINS OF PLASMA (A REVIEW).

Barr, D. P. *J. Chron. Dis.* **1:** 63 (Jan.) 1955.

Although the extent of lipid deposit in most arteries differs little in men and women, there is some precocity of its development in the coronary arteries of men. Angina pectoris, coronary occlusion, and myocardial infarction rarely occur in women before the age of 40. Arteriosclerotic disease of the vessels of the legs is more common in men. The susceptibility of men and the relative immunity of young women to serious consequences of coronary and peripheral atherosclerosis are not satisfactorily explained by anatomic differences in the sexes. The relative incidence of severe or fatal complications cannot be explained by any demonstrable variation with sex in the concentration of total lipids, cholesterol, or phospholipids. Sex-linked differences in the distribution of lipoproteins can, however, be demonstrated by Cohn fractionation of plasma or by the methods of paper electrophoresis and ultracentrifugation. Young men tend to have in their plasma a greater concentration of beta lipoproteins, a smaller amount of alpha lipoproteins, a higher beta-alpha ratio, and a larger content of S_f 10–20 lipoproteins. Action of heparin in clearing alimentary hyperlipemia is less prompt in young men. The number of mast cells in their tissues is less than in young women. These distinguishing features of sex are not apparent in the aged. Both the incidence of clinical complications and the distinctive differences in the state of lipids in the plasma are less prominent after the time of the menopause. That the chemical differences between young men and women have some relationship to the development of atherosclerosis is indicated by the demonstration that states of relative freedom from the disease are accompanied by lipid patterns like those of young women, and that diseases and conditions which are accompanied by advanced atherosclerosis or are known to be atherogenic have patterns that are exaggerations of those found in young men. In man the administration of gonadal hormones is accompanied by profound changes in the distribution of lipids in the plasma. Estrogen transforms the highly abnormal lipid pattern of myocardial infarction to one that is indistinguishable from that of healthy young women. Methyl testosterone exerts an opposite action: it exaggerates the lipid abnormality of survivors of myocardial infarction; it induces patterns similar to those of coronary atherosclerosis in individuals whose plasma has previously shown no lipid abnormalities. Contrary to the experience in the chick, the administration of androgens simultaneously with that of estrogens obliterates the chemical effects of the estrogens. The accumulated clinical and experimental evidence leaves little doubt that sex is a potent factor in the development of atherosclerosis, and that its influence is hormonal and is accompanied by easily recognizable changes in the distribution of lipids in plasma. There is much reason to believe that the development of coronary atherosclerosis and its complications is dependent upon factors not equally operative in other arterial systems. (Excerpt of author's summary.)

PROBENECID (BENEMID). ITS USES AND SIDE-EFFECTS IN 2,502 PATIENTS.

Boger, W. P., and Strickland, S. C. *A. M. A. Arch. Int. Med.* **95:** 83 (Jan.) 1955.

The uses and side-effects of probenecid in 2,502 patients, including a large series treated by the authors, are reviewed. Probenecid is administered chiefly by the oral route. It is rapidly absorbed from the gastro-intestinal tract, and is eliminated by glomerular filtration. The survey indicates that a daily dosage of as much as 2 Gm. of probenecid can be ad-

ministered safely for as long as four years. In patients with impaired renal function, the safe dosage is somewhat less. Probenecid therapy has been used most extensively in the treatment of chronic gout and in conjunction with oral penicillin therapy. The profound uricosuric action of probenecid may, by its effect on the biochemical equilibrium of the patient, precipitate an acute attack of gout. Apparently, about 10 per cent of patients with gout suffer an acute attack shortly after probenecid therapy is instituted. However, when therapy is continued, the frequency and severity of attacks of gout seem to diminish. Probenecid therapy seems to prevent the laying down of tophi and to cause uric acid deposits already present to diminish in size or disappear. When probenecid is used in conjunction with orally or parenterally administered penicillin, the penicillemia resulting from the dose of penicillin is increased from 2 to 10 times. A total of 175 side-effects were noted in the 2,502 patients. Intolerance of probenecid was most commonly indicated by gastro-intestinal symptoms, which occurred in 78 of the patients studied. Discontinuation of therapy was necessary in only 8 of these patients; in the majority, the gastro-intestinal symptoms were relieved by reducing the dosage. Hypersensitivity reactions occurred in 8 patients, and skin rashes were observed in 34. Some of the skin rashes were probably due to concurrent penicillin therapy. Drug fever was noted in 9 patients. Thirty-five of the 175 side-effects were related to the urinary tract, and perhaps should be regarded as evidences of the uricosuric activity of probenecid rather than as side-effects. No deaths have been attributed to probenecid therapy, and there is no evidence that probenecid aggravates pre-existent renal damage, causes hepatic toxicity, or suppresses the hemopoietic system.

RHEUMATOID ARTHRITIS: A REVIEW OF RECENT ADVANCES IN OUR KNOWLEDGE CONCERNING PATHOLOGY, DIAGNOSIS, AND TREATMENT (A REVIEW).

Bunim, J. J.; Sokoloff, L.; Williams, R. R., and Black, R. L. *J. Chron. Dis.* **1:** 168 (Feb.) 1955.

The pathologic changes in rheumatoid arthritis are discussed under the headings: joint structures, the subcutaneous nodule, tendons and bursae, heart, blood vessels, skeletal muscles, nervous system, eye, endocrine organs, hematopoietic system, visceral granulomata, and complications and miscellaneous changes. The development of serologic tests for rheumatoid arthritis and the Ziff modification of the hemagglutination test are outlined. The results obtained with various procedures in the hemagglutination test appear in tabular form. The effects of age, sex, activity, and duration and type of arthritis on the test are analyzed. The antirheumatic agents, cortisone, hydrocortisone, corticotropin, phenylbutazone, and gold are considered as to the nature of response, effect on lesions, dosage, results, limitations, contraindications, and toxicity.

MOLLUSCUM SEBACEUM.

Calnan, C. D., and Haber, H. *J. Path. & Bact.* **69:** 61 (Jan.–Apr.) 1955.

Molluscum sebaceum (kerato-acanthoma) is one of the various skin conditions that simulate squamous-cell carcinoma. Review of a series of 105 patients with molluscum sebaceum confirmed the impression that the condition is not malignant. The patients ranged in age from 15 to 78 years; the majority were between 40 and 70 years of age. In all but 1 of the patients, only one lesion was present. More than 80 biopsy specimens were examined microscopically. The lesion starts with hyperplasia of a group of follicles, which leads to hyperkeratosis and acanthosis with irregular downward growth to the sweat-gland level. The whole ectodermal part of the skin takes part in the formation of the lesion. Eventually growth ceases, and the lesion is destroyed by the ensuing inflammatory reaction. The usual clinical course was rapid growth of the lesion for four to eight weeks followed by slow involution over a period of two to four months. The lesion was present for longer periods in only 3 of the patients. Three of the patients had a history of mild trauma, and 6 were gas, tar or oil workers. Since the clinical features are remarkably uniform, diagnosis of

molluscum sebaceum is usually easy. The tumor is about 1 cm. in diameter and dome-shaped when fully developed. There is a central horny plug or crust. The smooth convex sides are not translucent, and fine telangiectatic vessels often occur on the surface. Molluscum sebaceum must occasionally be differentiated from true squamous epithelioma, senile or solar keratoma, and keratinizing verruca vulgaris. Spontaneous involution occurred in 17 of the patients. Treatment consists of curettage with galvano-cauterization of the base, simple local excision, or roentgen-ray therapy. Recurrences were observed in 2 patients after curetting or slicing. Treatment with roentgen rays is the simplest therapy. It is particularly advisable for elderly patients, since it causes the least local disturbance.

FOCAL PAGET'S DISEASE OF THE SKULL (OSTEOPOROSIS CIRCUMSCRIPTA).

Collins, D. H., and Winn, J. M. *J. Path. & Bact.* **69:** 1 (Jan.–Apr.) 1955.

A sharply outlined area of soft, rarefied, and congested bone, corresponding to the lesion radiologically identified as osteoporosis circumscripta, was found incidentally at necropsy in the skull of 5 patients dying in the hospital from causes unrelated to the bone disease. The histologic characters of the lesion in each case showed it to be a form of Paget's disease in which bone resorption greatly exceeded new bone formation. The skulls were little, if at all, thickened and were not deformed. The vault was generally affected more than the base, and the disease seemed to have spread fan-wise from either the frontal or the occipital pole. The ages of the patients ranged from 43 to 80. Four of the 5 were men. The incidence of osteoporosis circumscripta proved to be about 1 in every 350 or 400 adult necropsies. It is much less common than Paget's disease of the more usual pattern. Paget's disease was found elsewhere in the skeleton in only 1 of the 5 cases, but simple osteoporosis of senile type in the vertebrae was proved in 3 cases. Our studies support the contention that the initial lesion of Paget's disease is bone destruction. We tentatively suggest that the failure, in osteoporosis circumscripta, of the productive phase that generally follows in Paget's disease may be associated with the same influences that impair osteoblastic activity in senile osteoporosis. (From authors' summary.)

PHYSIOTHERAPY IN GERIATRIC REHABILITATION.

Cosin, L. *Brit. J. Phys. Med.* **58:** 25 (Feb.) 1955.

The functional rehabilitation of elderly patients is affected by pathologic, psychologic, and sociologic disturbances. The elderly patient may react emotionally to his increasing dependence upon others by feeling that his comfort depends upon the perpetuation of symptoms of disease. Feelings of insecurity due to loneliness are common in elderly persons. The sociologic problem of continued care must be solved before maximal physical recovery can be expected. The frequent occurrence of more than one pathologic process in the elderly patient deserves special consideration, for each process may hinder the attainment of painless, free, and voluntary movement. With the help of nurses, occupational therapists, social workers, and psychiatric social workers, an effective group approach to these problems is possible. After they have been adequately assessed and treated, the residual physical disability of the patient can be profitably handled on the basis of functional rehabilitation. Idiopathic rehabilitation involves restoration of function following disability due to a major pathologic process, such as fracture of the femur or rheumatoid arthritis. Heteropathic rehabilitation involves a general restoration of activity when there is a pathologic process affecting the efficiency of the body as a whole in addition to a specific disability.

SUR TRIOS CAS D'ANÉMIE DE BIERMER CHES DES VIEILLARDS (THREE CASES OF PERNICIOUS ANEMIA IN THE AGED).

Creyx, M.; Levy, J.; Destrem, H., and Buznic, A.-L. *J. méd. Bordeaux* **131:** 1253 (Nov.) 1954.

Pernicious anemia is less rare in the aged than texts have heretofore implied. Initially the symptomatology may be confused with that of senile cachexia or occult carcinoma. Its

characteristics are severe digestive disturbances, extreme asthenia, edema of the extremities or face, pallor with a slightly yellow aspect, and more or less pronounced dyspnea on effort. Neurologic signs are not uniformly present. Gastric achylia, however, is usual, coincides with low erythrocyte counts, and varies in intensity with the severity of the disease. It is also characterized by sudden onset and by the rapidity of its evolution in the absence of specific therapy. The hemogram is the same as at other ages. The response to specific therapy is as favorable as in younger adults. The 3 elderly patients with pernicious anemia described responded to vitamin B_{12}, folic acid, and dyspeptin.

DISORDERS OF CALCIUM AND PHOSPHORUS METABOLISM—THEIR DIFFERENTIAL DIAGNOSIS.

Hamlisch, R. E. *M. Times* **83:** 139 (Feb.) 1955.

An outline is given of present knowledge of normal calcium and phosphorus metabolism and of the action of vitamin D, AT10, and parathyroid hormone. The author points out common situations in which a calcium and phosphorus disorder may be present, and separates them according to origin, as follows: gastro-intestinal, urinary, bone, neurologic, menopausal, ophthalmologic, metastatic calcification, tumor in the neck, and hematologic. Laboratory aids in differential diagnosis of disorders of calcium and phosphorus metabolism include 1) serum examinations (Ca, P, alkaline phosphatase, NPN, A/G ratio, CO_2, Cl, Na, K, uric acid, vitamin A, carotinoids, and prothrombin time), 2) urinary examinations (routine urinalysis, Ca, Bence-Jones protein, titratable acidity, NH_4 ions, amino acids, urea clearance, and PSP), 3) heart examinations (EKG, to discover serum Ca and K abnormalities), 4) fecal examinations (for Ca, fat and N), 5) slit-lamp examinations of the eye for calcium deposits in the cornea, 6) biopsy of bone, and 7) x-ray examinations of the neck and mediastinum, kidneys, skull, teeth, vertebral column, long bones, and pelvis. A good approach from a laboratory standpoint consists of determining the calcium, phosphorus, alkaline phosphatase, and nonprotein nitrogen levels of the serum, determining the urinary calcium, performing a urinalysis, and securing roentgenograms of the vertebrae and skull—proceeding with further examinations if these tests show abnormalities. The characteristics of the following diseases are described, and the laboratory findings in each are presented in tabular form: 1) primary hyperparathyroidism, 2) secondary hyperparathyroidism, 3) hypoparathyroidism, 4) pseudohypoparathyroidism, 5) osteomalacia (due to vitamin D deficiency), 6) renal tubular acidosis, 7) Fanconi syndrome, 8) idiopathic hypercalciuria, 9) osteoporosis, 10) polyostotic fibrous dysplasia, 11) Paget's disease, 12) Paget's disease immobilized, 13) multiple myeloma, 14) diseases with invasion of bone causing excessive bone destruction, 15) hypervitaminosis D, 16) syndrome due to excessive milk and alkali intake, and 17) osteogenesis imperfecta.

MASSIVE GASTROINTESTINAL HEMORRHAGE DUE TO FAMILIAL-HEREDITARY TELANGIECTASES.

Hardt, L. L.; Steigmann, F.; Levinson, S. A., and Gore, I. *Gastroenterology* **28:** 70 (Jan.) 1955.

Frequent bleeding from the nose, skin lesions, or the gastro-intestinal tract may be caused by familial hemorrhagic telangiectasia. This diagnosis is strongly supported by a history of bleeding episodes in members of the patient's family. Case reports of 6 patients with bleeding from the gastro-intestinal tract due to hereditary hemorrhagic telangiectasia are presented. The patients, 5 males and 1 female, were from 46 to 69 years of age. A family history indicating telangiectasia was obtained in 3 patients. The bleeding tendency appeared in 5 of the patients when they were over 40 years of age. All 6 patients had a history of melena. Four had hematemesis; 2 had nosebleeds, and 1 had hematuria. Symptoms suggestive of peptic ulcer were present in only 3 patients. Except for anemia, the blood findings in all the patients were normal. Proctoscopic examination was carried out in 3 patients but revealed the telangiectasia in only 1. Gastroscopic examination, which was also per-

formed in 3 patients, yielded no positive results. Three of the patients died—2 as a direct result of hemorrhages and 1 from hepatitis following blood transfusions necessitated by profuse gastric bleeding. At postmortem examination, telangiectases were found throughout the gastro-intestinal tract and on the skin, the oropharynx, and the larynx. In the surviving patients, telangiectases were observed in the buccal cavity, the nose, the recto-sigmoid area, the bladder, and the liver, and on the face, nose, and chest. The treatment of hereditary hemorrhagic telangiectasia consists largely of an adequate non-irritating diet with a high protein content, and large doses of iron. The patient should avoid excessive physical strain, and the bowels should be kept open to prevent straining at the stool. Oral rutin therapy may be of benefit.

THE PROBLEM OF THE AGING FACE.

Johnson, J. B. *Plastic & Reconstr. Surg.* **15:** 117 (Feb.) 1955.

The changes that occur in the skin during senescence are primarily atrophic. They include loss of contractility, fragmentation and basophilic degeneration of the elastic fibers, and fragmentation and hyalinization of the collagen fibers. These changes are progressive and cannot be combatted permanently. Rhytidectomy offers an opportunity for a temporary change in the appearance of the face and neck. The greatest improvement can be expected in patients with a predominance of redundant skin in the upper neck. For maximum improvement, obese patients should undergo a reducing program prior to surgery. Emotionally unstable patients are not suitable subjects. Features of the various rhytidectomy procedures for the face and neck, removal of the submental fat pad, and the removal of glabellar frown lines and of redundant skin from the upper and lower lids are outlined. Procedures for the removal of horizontal forehead lines should be discouraged, as these return rapidly. The removal of frown lines in the glabellar region requires the excision of redundant skin. No attempt should be made at complete removal of lines in the cheeks as this produces a fixed expression. Rhytidectomy cannot eliminate small perpendicular lines on the upper and lower lips. Some of the procedures, as on the face and neck, may be performed at the same time. General anesthesia is preferable. The procedure on the lower eyelids is carried out separately under local anesthesia.

REHABILITATION PROBLEMS CONCERNING ELDERLY AMPUTEES.

Langdale-Kelham, R. *Brit. J. Phys. Med.* **18:** 27 (Feb.) 1955.

Elderly patients who have had lower extremity amputations may be considerably benefited by an artificial limb. Return to useful employment, elimination of the need for constant care, and alleviation of the mental shock resulting from amputation may result. A statistical analysis of 344 patients over 65 years of age showed that in 4.0 per cent, no limb fitting was attempted, as it was considered that the strain would be dangerous; in 9.0 per cent, death occurred within six months after discharge; in 29.4 per cent, rehabilitation failed; in 49.7 per cent, who were making regular use of their limbs six months after discharge, rehabilitation was successful; and in the remaining 7.9 per cent, the limbs were used occasionally. Age alone did not seem to determine the degree of success. Of the 171 patients who were successfully rehabilitated, 7 were between 80 and 84 years of age and 3 were 85 years of age or older. The first step in rehabilitation at the limb center is evaluation of the patient's physical condition and mental state. To correct the physical debilitation that often results from long periods of hospitalization, groups of patients engage in general remedial exercises designed to mobilize the joints and the spinal column, to eliminate flexion deformities, and to strengthen the muscles. After about ten days, single limb amputees with amputation above the knee are fitted with light-weight pylons. Bilateral thigh amputees start with Rocker Peg legs. The shortness of these legs gives the patient confidence and aids him in gaining balance. In training for walking, the patient first learns to take weight upon the limb or limbs while standing within the walking rails. Eventually he progresses to the use of walking sticks and learns the techniques involved in turning, sitting

down, falling, and regaining the erect position. Fully articulated permanent legs are then prescribed for those patients who are physically and mentally capable of controlling them. For some bilateral thigh amputees, a permanent type of pylon or Rocker Peg leg is most suitable. Single thigh amputees receive the light-weight metal leg. This is often fitted with a semi-automatic knee lock, which provides a safety factor appreciated by most elderly patients. Patients with amputation below the knee receive permanent legs of wood or metal as soon as the remedial exercise training and stump preparation are completed. During training for walking with the permanent limb, changes are likely to occur in the stump that necessitate immediate correction of the fit of the prosthesis. A follow-up program is essential for elderly patients, who may have a relapse when not provided with the encouragement received during training. Elderly patients with amputation of an upper extremity present a much smaller rehabilitation problem. Fewer patients are involved, and the artificial arm is not a weight-bearing prosthesis. Remedial exercises, opportunity to observe patients successfully using prostheses, arm training, and follow-up help are important in rehabilitation. Temporary artificial arms are not necessary. Patients who at first want a "cosmetic" arm may be persuaded, by example and encouragement, to use a "light working" type.

GLANDES ENDOCRINES ET SÉNESCENCE (THE ENDOCRINE GLANDS AND SENESCENCE).

Laroche, A. C. *Concours méd.* **77:** 439 (Jan. 29) 1955.

During senescence the endocrine glands undergo the same pathologic processes as other tissues, although the rate of involution varies. Thus, the gonads appear to age more rapidly than the anterior pituitary and the adrenals. In the aged, ACTH and thyroid-stimulating hormone production appear to be normal but the FSH level is high, especially in the female, up to an advanced age. The thyroid undergoes partial inhibition after age 60. The basal metabolism and heat expenditure are lowered; the level of plasma iodine remains normal and that of blood cholesterol is slightly diminished. No true hypothyroidism exists but there appears to be an adaptation to reduced needs of the body. Adrenocortical hyperplasia is frequent and occurs at the expense of the zona fasciculata. 11-Oxysteroid excretion is normal; the cortex responds to ACTH; and the function of the pituitary-adrenal axis is preserved. Androgenic hormone excretion is diminished due to involution of the gonads and to a diminished secretion of adrenal components. In the male, gonadal involution is slow and sexual decline depends not only upon testicular regression but also on the retardation of physiologic and psychic functions. The arrest of maturation of spermatozoids is late. Involution of the ovary is precocious but hormone assays and vaginal smears show the presence of follicular hormone well after the menopause. The decline in gonadal secretions has repercussions on the general metabolism and particularly on the secondary sex characteristics, the trophicity of the skin, and osseous calcification. In aged subjects, the derivatives of testosterone raise the metabolic rate and relieve disturbances in physical and psychic function; estrogens have a less pronounced effect. A truly preventive and curative therapeutic regimen for senescence will be one combining small physiologic doses of thyroidal, gonadal, and adrenal hormones.

THE SENILE NAIL.

Lewis, B. L., and Montgomery, H. *J. Invest. Dermat.* **24:** 11 (Jan.) 1955.

The nails of the fingers and toes in many elderly persons show distinctive changes. The gross features are dullness, opacity, increased longitudinal ridging, changes in color, alterations in thickness, and masking of the lunula. Microscopic study of 6 specimens of senile nails showed that the histologic features also differed from those in the mature nail. The specimens examined histologically were 5 fingers and 1 toe removed from limbs amputated because of malignant lesions involving their proximal portions. The toe was from a patient 52 years of age; all the fingers were from patients 70 years of age or more. The

features observed in the nail included ridging, changes in thickness, an increase in pertinax bodies, terminal splitting, peculiarities when studied with the von Kossa stain for calcium, and irregularities in the proximal nail generative region. In the nail bed, thickening of the walls of blood vessels with or without changes in elastic tissue was observed. Senile cutaneous changes, including merging of elastic and connective tissue in the cutis, were also seen.

STUDIES IN CEREBROVASCULAR DISEASE. I. THE SYNDROME OF INTERMITTENT INSUFFICIENCY OF THE BASILAR ARTERIAL SYSTEM.

Millikan, C. H., and Siekert, R. G. *Proc. Staff Meet., Mayo Clin.* **30:** 61 (Feb. 23) 1955.

Ten cases are described in which strange intermittent attacks were characterized by symptoms that indicated transitory impairment of function in some portion of the pons, mesencephalon or occipital lobes. The clinical picture of thrombosis of the basilar artery developed in 3 of the patients and was confirmed at necropsy. These attacks may be a result of temporarily inadequate blood flow through the basilar arterial system and it is suggested that the episodes be called the syndrome of intermittent insufficiency of the basilar arterial system. This is a new concept of a disorder that has been in existence for an unknown period. The symptoms in the 10 patients described included loss of vision, double vision, ptosis, clouding of consciousness, confusion, unconsciousness, hemiparesis and hemiplegia, dysarthria, dysphagia, sensory phenomena in the face or one extremity or half of the body, vertigo, tinnitus, vomiting, unsteadiness, and headache. The same symptom on opposite sides of the body in definite attacks, and in the absence of a more likely cause after neurologic investigation, suggests the diagnosis. This diagnosis is probably correct when such alteration of position is also associated with such phenomena as dimness of vision, dysarthria, dysphagia, or vertigo. Attacks can be terminated by the administration of anticoagulant drugs, which fact offers a clue to the as yet undetermined pathogenesis of the syndrome. Although the prognosis appears to be serious, the natural history of the attacks is not known.

THE ROLE OF THE ADRENAL CORTEX IN PROSTATIC CANCER.

Morales, P. A.; Brendler, H., and Hotchkiss, R. S. *J. Urol.* **73:** 399 (Feb.) 1955.

The effects of bilateral total adrenalectomy in 20 patients with advanced prostatic cancer, with or without secondary dissemination of the disease, are reviewed. Bilateral adrenalectomy was performed in 11 patients who had a relapse following castration and estrogens. The remaining 9 had intact testes and had never received estrogen therapy prior to adrenalectomy. The latter group provided an opportunity to study the role of the adrenal cortex *per se* in prostatic growth. Eighteen patients were available for critical evaluation. Eleven are still alive. Of 10 patients who complained of pain initially, complete relief was experienced in 4, partial in 5, and none in 1. Symptoms of urinary obstruction were lessened in 9 patients and unrelieved in 9. Seven patients showed significant increases in body weights, despite the presence of extensive metastasis in 4. A regression in the local growth was noted in 1 patient. No regression of the osseous metastasis as judged by x-ray findings was observed in any of the patients. A comparison of the clinical response observed in patients subjected to pre- and post-castration adrenalectomy showed no remarkable difference between the two groups. Bilateral adrenalectomy has been shown to provide a definite measure of subjective relief in at least 40 to 50 per cent of patients who otherwise would remain in a state of relapse until their deaths. The procedure has also proved to be a safe and simple one in patients who are reasonable surgical risks. It should be performed in suitable patients in whom there has been a relapse after castration and estrogen administration. (From authors' summary.)

CLINICAL SYNDROMES ASSOCIATED WITH HYPERNATREMIA.

Schoolman, H. M.; Dubin, A., and Hoffman, W. S. *A. M. A. Arch. Int. Med.* **95:** 15 (Jan.) 1955.

More than 100 instances of hypernatremia (hyperosmolarity) in acutely ill patients were encountered during a four-year period. Most of the cases fell into one of three general categories, based on the mechanism producing the hypernatremia and the clinical syndrome associated with it. Of the patients in the primary desiccation group, 15 were infants (all under 2 years of age) with mild diarrhea. They were listless, irritable and dehydrated. In 18 patients, usually elderly, the underlying disease precluded their adequately caring for themselves. Their condition at the time of hypernatremia was characterized by dry skin, moderate tachypnea, torpor or stupor, hyperthermia and, occasionally, muscular irritability. No localizing neurologic signs were present. Moderate elevation of the blood nonprotein nitrogen level was always present, in addition to elevation of the serum sodium and chloride levels. A slight elevation of the blood creatinine concentration was also observed. The serum potassium concentration was usually in the high normal range but sometimes was even lower than normal. In 63 of the patients, the acute hypernatremia was associated with injury of the central nervous system. Forty-three of these patients were 60 years of age or older. In the majority, the lesion was encephalomalacia and hemorrhage. All the patients were in a coma or semicoma on hospital admission. In 5 patients who had glycosuria and acetonuria, the coma was falsely ascribed to diabetic acidosis. The possibility that intracranial pathology rather than diabetic acidosis is the cause of coma should be suspected when tachycardia and Kussmaul breathing are absent, blood pressure levels are adequate, and anisocoria or ophthalmoplegia and a moist skin are present. In patients with these findings, ketosis is probably due to starvation. Hypernatremia was associated with diabetic coma after saline therapy in 9 patients. These patients were comatose or semicomatose on hospital admission and were treated with insulin and salt solution. Hypernatremia developed within twenty-four hours. A discussion of the possible mechanisms involved in the production of hypernatremia is presented. In the case of elderly patients in the primary desiccation category, incapacitation precludes adequate oral water intake and predisposes to hypostatic pneumonia. Hyperthermia and tachypnea contribute to the water loss, which is intensified during severely hot weather. In addition, elderly patients may have degenerative vascular changes in their kidneys that limit concentrating power. Water loss through Levine suction, vomiting, and diarrhea may occur. The treatment of hypernatremia consists of intravenous or oral administration of non-saline fluids. This therapy is usually successful, except in patients with central nervous system injury severe enough to produce death.

THE ROLE OF HYPERTENSION IN THE ETIOLOGY AND PROGNOSIS OF CORONARY OCCLUSION.

Sigler, L. H. *Ann. Int. Med.* **42:** 369 (Feb.) 1955.

A series of 1,160 patients with coronary occlusion was reviewed in an effort to determine whether or not hypertension affects the incidence or alters the prognosis of coronary occlusion. The series included 946 males and 214 females. Although the ratio of males to females in the series was about 4.4 to 1, the percentage of female patients with hypertension was almost twice as great as the percentage of male patients with hypertension. The patients were divided into groups according to sex, blood pressure levels, and the decade in which the first attack of coronary occlusion occurred. The blood pressure groups were as follows: Group I, systolic up to 140, diastolic up to 90; Group II, systolic 141–160, diastolic 91–100; Group III, systolic 161–200, diastolic 101–110; Group IV, systolic above 200, diastolic above 110. Coronary occlusion appeared earlier in the males than in the females. The incidence was highest between 50 and 59 years of age in males; in females, the peak incidence was

between 60 and 69 years. Although the incidence of hypertension also increased with age, it did not correspond to the increase in coronary occlusion. Relatively more males than females belonged to the lower blood pressure groups at the time of the first attack of coronary occlusion. Analysis of the 363 deaths showed that though there was a progressive increase in deaths following coronary occlusion with advancing age, this increase did not correspond to the increase in blood pressure. A larger percentage of males than of females lived for more than one, five, and ten years following the first attack. The percentage of females with hypertension who survived these periods was greater than the percentage of those with normal levels. The study showed no definite causal or prognostic relationship between hypertension and coronary occlusion. The findings indicated that the incidence of hypertension in a series is affected by the ratio of male to female patients as well as by the relative ages of the patients.

ADVANTAGES OF TRANSURETHRAL REMOVAL OF CERTAIN BLADDER TUMORS.
Thompson, G. J., and Kaplan, J. H. *J. Urol.* **73:** 270 (Feb.) 1955.

From recent experience and a review of 300 cases, transurethral resection is concluded to be the preferable procedure for removal of a bladder tumor of high-grade malignancy that has not infiltrated beyond the bladder wall and can be accurately delineated. It also is preferable for removal of the visible portion of tumors that have infiltrated the perivesical tissues, and should in these cases be followed by irradiation to destroy any microscopic portions remaining. The technic is described. Postoperatively, catheter drainage is established and urinary antiseptics or antibiotics used. Improvement in bladder function, with relief of frequency and cessation of hematuria and tenesmus usually occurs promptly. The bladder wall heals well, and there is little scar tissue formation or contracture and no appreciable reduction of bladder capacity. The five-year survival rate in the reported series of patients treated by transurethral surgical operation plus selective irradiation was better than in patients treated by open surgical methods. Cystectomy, however, may be more advantageous when the extent of a highly malignant tumor cannot be determined accurately by cystoscopy and when tumors of low grade occur with great rapidity in growth and number.

PRIMARY CARCINOMA OF THE URETER: A PATHOLOGIC AND PROGNOSTIC STUDY.
Whitlock, G. F.; McDonald, J. R., and Cook, E. N. *J. Urol.* **73:** 245 (Feb.) 1955.

A workable classification of carcinoma of the ureter is presented, which has practical prognostic significance. It is based on the pathologic study of 33 cases and is similar to classifications already proved useful in carcinoma of the renal pelvis and urinary bladder. In this series, 55 per cent of the tumors were purely papillary in structure, 29 per cent were papillary and infiltrating, and 16 per cent were nonpapillary and infiltrating. About half (51.5 per cent) of the ureteral carcinomas were of low histologic grade (grades 1 and 2) and about half (48.5 per cent) were of high-grade malignancy (grades 3 and 4). The majority (83.2 per cent) of pure papillary carcinomas were of a low degree of malignancy and the majority of papillary and infiltrating and pure infiltrating carcinomas were of a high degree of malignancy (85 per cent grades 3 and 4). Venous and lymphatic involvement occurred in this series only with carcinomas showing infiltration. The frequency with which such involvement was found in this study is undoubtedly lower than the actual incidence. At least half of the papillary carcinomas of the ureter were associated with, or followed by, similar carcinomas in the bladder. The nonpapillary tumors did not exhibit this tendency. Of the 33 cases, there were 10 in which bladder tumors developed after removal of the primary carcinoma of the ureter. This fact makes it advisable to carry out regular, routine postoperative cystoscopic check-ups, to the same degree that we are now following up cases of carcinoma primarily in the bladder. The prognosis of low-grade papillary tumors

of the ureter is good. The prognosis of high-grade tumors showing evidence of infiltration is extremely poor. Of the patients with papillary carcinoma, 66.7 per cent lived five or more years. Only 1 patient with an infiltrating carcinoma lived as long as three years, and he was not cured. Of the patients with a grade 1 or 2 carcinoma, 77.7 per cent lived five or more years. No patient with a grade 3 or 4 cancer lived as long as three years. The average length of life of patients who died after operation in the two groups of carcinomas showing infiltration was about eleven months. It is apparent from the foregoing evidence that the standard operation of complete nephro-ureterectomy, as practiced today, is adequate and satisfactory for the treatment of the papillary types of carcinoma of the ureter. It is apparent, on the other hand, that patients with infiltrating carcinoma of the ureter are not being cured by present-day methods of surgery. Whether more complete dissection of the regional lymphatics would offer a higher rate of cure remains to be seen. (From authors' conclusions.)

PROSTATIC CARCINOMA INVOLVING THE RECTUM. THE PROBLEM OF DIFFERENTIATION FROM OTHER MALIGNANT LESIONS.

Winter, C. C. *California Med.* **82:** 85 (Feb.) 1955.

The records of two general hospitals for a period of thirty months showed approximately 150 cases of prostatic cancer. In 13 patients, the prostatic carcinoma involved the rectum. The author's classification for this type of cancer, with the number of patients found in each category, is as follows: 1) occluding rectal lumen, 2; 2) annular, perirectal lesion, 6; 3) invading rectal mucosa, 3; 4) separate metastasis to the rectosigmoid, 2. Histologic examination of an adequate biopsy specimen is the final determinant in the diagnosis of prostatic cancer. Additional information may be gained from serum phosphatase levels, from tissue assays for acid phosphatase activity, from cytologic examination of the prostatic smear or urine sediment, from cystoscopy and sigmoidoscopy, and from roentgenologic examination of the bones, lungs and gastro-intestinal tract. Case histories of 5 patients from 59 to 69 years of age illustrate the problems encountered in diagnosis. In 2 instances, the difficulty lay in differentiating prostatic from rectal carcinoma. In a patient who had carcinoma of the prostate with bone metastasis, histologic evidence was difficult to obtain. One of the patients had carcinoma of the urinary bladder involving the rectum, which simulated cancer of the prostate or rectum. Once carcinoma of the rectum has been diagnosed as prostatic in origin, palliative medical and surgical therapy should be begun. The disease is incurable in the advanced stage. Neither radical pelvic operation nor colostomy are likely to be advisable. The most effective treatment at present seems to be the combination of castration and estrogen therapy.

1957 ANNUAL MEETING

AMERICAN GERIATRICS SOCIETY

Waldorf-Astoria,
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May 30 and 31, 1957

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